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THE UNIVERSITY OF ALBERTA

1,5-METHANO[10]ANNULENE.
NEW C-ACYLATION.

by

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A THESIS

SUBMITTED TO THE FACULTY OF GRADUATE STUDIES AND RESEARCH

IN PARTIAL FULFILMENT OF THE REQUIREMENTS FOR THE DEGREE

OF DOCTOR OF PHILOSOPHY

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EDMONTON, ALBERTA

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THE UNIVERSITY OF ALBERTA

FACULTY OF GRADUATE STUDIES AND RESEARCH

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1,5-METHANO[10]ANNULENE.

NEW C-ACYLATION.

submitted by Dee W. Brooks in partial fulfilment of the requirements for the degree of Doctor of Philosophy.

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ABSTRACT

PART I

The synthesis of 1,5-methano[10]annulene was undertaken with the objective of producing a good model for a presently hypothetical, neutral, monocyclic, and planar 10π-electron system. On the basis of Hückel molecular orbital theory or more simply the "4n+2" rule, a monocyclic, planar arrangement of 10π-electrons was predicted to exhibit aromatic properties. The lability exhibited by the two monocyclic[10]-annulenes 4 and 5 was in contrast with the aromatic properties of other 10π-electron systems such as naphthalene 18, azulene 17, and 1,6-methano-[10]annulene 15. These latter three compounds do not provide true models of a monocyclic 10π-electron system due to various bonding interactions such as; the C9,10 π and σ bonding in 18, the C9,10 σ bonding in 17, and a possible C1,6 transannular bonding interaction in 15. 1,5-Methano [10]annulene is expected to have minimal transannular bonding interactions, and therefore its physical properties may reflect those of a monocyclic 10π-electron system if the molecule can assume a planar geometry.

The key step in the synthesis of the required skeleton involved a Michael-Wittig reaction between cycloocta-2,4,6-trienone 64 and the anion of methyl-4-(dimethylphosphinyl)-2-butenoate 72 to give, after a base catalyzed rearrangement, 8-methoxycarbonylbicyclo[5.3.]-undeca-1,3,5,8-tetraene 74. A series of steps led to bicyclo[5.3.1]-undeca-1,3,5,9-tetraene-8-one 76 which was reduced to the corresponding *endo*-alcohol 110. Epimerization of 110 to the *exo*-alcohol 116 and pyrolytic elimination of the corresponding *p*-nitrophenylcarbamate gave 1,5-methano[10]annulene 19 as an air sensitive orange oil which decomposed slowly at room temperature. Several substituted derivatives

of 19 were also prepared and their properties are reported.

The physical properties of 1,5-methano[10]annulene were consistent with a highly delocalized arrangement of 10π-electrons. A comparison of the properties of 19 and those of the 10π-electron systems 15, 17 and 18 is made. The absence of exact geometric data for 19 precludes any quantitative discussion of its electronic structure. However, on the basis of the observable properties which are reported it is concluded that 1,5-methano[10]annulene, possibly, represents the best model yet prepared for a monocyclic, 10π-electron system and indeed demonstrates that a delocalized array of 10π-electrons does provide a stabilized "aromatic" system as originally predicted by Hückel's theory.

PART II

During the course of investigations directed toward the synthesis of polyoxo-macrolide antibiotics it became apparent that a method to effect a mild C-acylation on acid and base sensitive synthetic intermediates would greatly facilitate the synthesis of this important class of natural products and related acyclic systems. A satisfactory solution for mild C-acylation, which has wide synthetic applicability, is described, and patterns to some extent a similar process which occurs in the biosynthesis of fatty acids.

The conversion of a carboxylic acid to the corresponding β-keto ester is operationally quite simple. Carbonyldiimidazole converts the acid into the corresponding acid imidazolide which is without isolation treated with the neutral magnesium salt of a malonic or methylmalonic half acid ester. The latter reagent is readily prepared from equivalent amounts of magnesium ethoxide and the respective half acid ester. The

C-acylation proceeds in quantitative or excellent yields and is normally complete within 16 h below 35°C. The wide scope of this reaction is demonstrated by the preparation of a variety of β-keto esters containing various functionalities. A modified procedure for C-acylation in the presence of a primary hydroxy group is also given. Although the mechanism of this new C-acylation is yet unknown, a discussion of some observations in this context and also possible biosynthetic implications of this reaction are offered.

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TABLE OF CONTENTS

	PAGE
ABSTRACT	v
ACKNOWLEDGEMENTS	viii
LIST OF TABLES	xi
LIST OF FIGURES	xii

PART I

1,5-METHANO[10]ANNULENE

CHAPTER

1.	INTRODUCTION	1
	A. THE CONCEPT OF AROMATICITY	1
	B. CRITERIA FOR AROMATICITY	3
	C. CYCLIC π-ELECTRON SYSTEMS	6
2.	THE 10π-ELECTRON SYSTEM	13
	A. THE MONOCYCLIC 10π-ELECTRON SYSTEM	13
	B. THE 1,5-BISDEHYDRO[10]ANNULENE SYSTEM	15
	C. THE 1,6-METHANO[10]ANNULENE SYSTEM	17
3.	SYNTHETIC APPROACHES TOWARD 1,5-METHANO[10]ANNULENE	20
4.	THE CONSTRUCTION OF THE 1,5-METHANO[10]ANNULENE SKELETON	28
5.	THE SYNTHESIS OF 1,5-METHANO[10]ANNULENE	70

PAGE

6. THE PHYSICAL PROPERTIES OF 1,5-METHANO[10]ANNULENE 81

A. ^{1}H NMR SPECTRAL ANALYSIS 81

B. ^{13}C NMR SPECTRAL ANALYSIS 90

C. ULTRAVIOLET AND VISIBLE SPECTRA 100

D. PHOTOELECTRON SPECTRA 103

E. CONCLUSION 107

7. EXPERIMENTAL 111

REFERENCES AND NOTES 162

PART II

NEW C-ACYLATION

CHAPTER

1. INTRODUCTION 176

2. THE BIOSYNTHESIS OF FATTY ACIDS 178

3. MODEL SYSTEMS FOR C-ACYLATION 186

4. MILD C-ACYLATION 200

5. EXPERIMENTAL 212

REFERENCES AND NOTES 235

LIST OF TABLES

PART I

1,5-METHANO[10]ANNULENE

TABLE		PAGE
1.	Induced Ring Currents in Annulenes	9
2.	Induced Diamagnetic Ring Current in Tetra-*tert*-butyl-didehydro[4n+2]annulenes	9

PART II

NEW C-ACYLATION

TABLE		
1.	Conversion of Carboxylic Acids into β-Ketoesters	203

LIST OF FIGURES

PART I

1,5-METHANO[10]ANNULENE

FIGURE		PAGE
1.	Some Charged $(4n+2)\pi$-Electron Systems	11
2.	A Synthetic Approach to 1,5-Methano[10]annulene	26
3.	The ^1H NMR Spectra of the Products A, B, and C from the Intramolecular Wittig Cyclization of Trieneone 64 and the Anion of Phosphonate 72 and Subsequent Purification Procedures	32-34
4.	100 MHz ^1H NMR Decoupling Experiments for 73	36
5.	100 MHz ^1H NMR Decoupling Experiments for 74	38
6.	100 MHz ^1H NMR Decoupling Experiments for 82	45
7.	100 MHz ^1H NMR Decoupling Experiments for 83	46
8.	100 MHz ^1H NMR Spectrum of Bicyclo[5.3.1]undeca-1,3,5,9-tetraene-8-one 76	51
9.	Shift Reagent Study of Bicyclo[5.3.1]undeca-1,3,5,9-tetraene-8-one 76	52
10.	100 MHz ^1H NMR Spectrum of the Silyl Enol Ether 88	55
11.	100 MHz ^1H NMR Decoupling Experiments for 88	56
12.	100 MHz ^1H NMR Spectrum of 94	62
13.	Pyrolysis Apparatus	64
14.	100 MHz ^1H NMR Spectrum of 8-Methoxycarbonylbicyclo-[5.3.1]undeca-1,3,5,7,9-pentaene 98	66
15.	100 MHz ^1H NMR Decoupling Experiments for 110	72

16. 100 MHz ^{1}H NMR Spectra of *endo*-110 and *exo*-Bicyclo [5.3.1]undeca-1,3,5,9-tetraene-8-ol 116 77

17. 270 MHz ^{1}H NMR Spectrum of 1,5-Methano[10]annulene 82

18. 270 MHz ^{1}H NMR Decoupling Experiments for 1,5-Methano-[10]annulene 83

19. Generated (ITRCAL) Spectra of the Decoupled AB_2 System in 19 85

20. Generated (ITRCAL) Spectra of the AB_2X_2 System in 19 86

21. The Induced Diamagnetic Ring Current in 1,5- and 1,6-Methano[10]annulene 88

22. ^{1}H NMR Spectra and Vicinal Coupling Comparison 91

23. 22.63 MHz ^{13}C NMR Spectrum of 1,5-Methano[10]annulene with Assignments 93

24. Selective ^{1}H Decoupling of the ^{13}C NMR Spectrum of 1,5-Methano[10]annulene 95

25. ^{13}C Chemical Shift Comparison 96

26. Compilation of ^{13}C Chemical Shifts 98-99

27. Absorption Spectra Comparison of 10π-Electron Systems 101

28. Absorption Spectra of Various Substituted 1,5-Methano[10]annulenes 102

29. Photoelectron Spectra of 1,5-Methano[10]annulene 19 and Azulene 17 104

30. Photoelectron Spectra of 1,6-Methano[10]annulene 15 and Naphthalene 18 105

PART II

NEW C-ACYLATION

FIGURE		PAGE
1.	The Sequence of Reactions for Fatty Acid Biosynthesis	179
2.	A Hypothetical Scheme for the Function of the Fatty Acid Synthetase Complex	181
3.	Proposed Mechanisms for the Biological C-Acylation in Fatty Acid Biosynthesis	183
4.	Proposed Mechanism for the Formation of 23	195
5.	Proposed Mechanism for the Formation of 27	197
6.	Choice of the Acyl Group for C-Acylation	208

PART I

1,5-METHANO[10]ANNULENE

CHAPTER 1

INTRODUCTION

A. THE CONCEPT OF AROMATICITY

Over several decades organic chemists have undertaken the synthesis of novel molecules whose properties might lead to a better understanding of the concept of aromaticity. This concept was introduced at a very early stage in the history of chemistry and has therefore evolved through different meanings and interpretations.[1] In the early nineteenth century, the term "aromatic" was used to classify organic compounds on the basis of odour. As analytical methods developed it was recognized that many of these odoriferous compounds were derivatives of benzene. The sensory description of aromaticity was replaced by a meaning based on composition and structure. In 1865 Kekulé suggested a symmetrical hexagonal structure for benzene[2] and later revised this to a dynamic structure consisting of two interchanging forms 1 and 2.[3]

1 2 3

Erlenmeyer suggested that the concept of aromaticity should not be limited to a common structural feature such as benzene, but rather, should include all substances of similar properties.[4] Aromaticity thus developed as a means of relating certain organic compounds which exhibited chemistry similar to benzene. Therefore, aromaticity

became identified with the stability of the benzene nucleus and its preference for substitution versus addition reactions. As ideas concerning the chemical bond were developed in the early 1900's,[5] it was recognized that the electron organization of aromatic compounds was different from that of double bonds in aliphatic compounds. In 1925, Armit and Robinson[6] suggested the inscibed circle formula 3 for benzene and formulated the concept of the "aromatic sextet" of electrons as being a stable association which was responsible for aromatic character.

The concept of π-electron molecular orbitals introduced by Hückel in 1931,[7] provided a theoretical foundation for the description of the electronic structure of benzene. His famous "4n + 2" rule extended the concept of aromaticity to other π-electron systems and resulted in a new meaning for aromaticity based on electronic structure. Theoretical treatments of aromatic systems by the molecular orbital[8] and valence bond[9] methods led to the calculation of resonance or electron delocalization energies. With this development, chemical reactivity was replaced by electron delocalization or resonance energy as a criterion for aromaticity.

It is a difficult task to define aromatic character in terms of experimentally measurable properties as no single physical criterion has been found as a definitive measure of aromaticity.[10] Aromaticity is generally accepted as a ground state property of a molecule which reflects a characteristic electronic structure involving delocalized π-electrons around a cyclic, planar, σ-framework. Any property of a molecule which provides information about electron organization is a potential measure of aromaticity. The classification of a given mol-

ecule as "aromatic" very often relies on a subjective judgement based on a combination of observable properties.

B. CRITERIA FOR AROMATICITY

Several observable properties of a molecule serve as criteria for aromatic character and they can be categorized as 1) structural, 2) thermochemical, and 3) spectroscopic.

1) Structural Criteria for Aromaticity

Two factors with respect to the geometry of a molecule are important in providing evidence for aromatic character : 1) a planar array of sp^2 hybridized carbon atoms and 2) equal C-C bond lengths. A coplanar system is necessary for effective π-bond overlap and any distortion from planarity will, in principle, give less delocalized character. The C-C bond lengths of aromatic compounds should be "like benzene" in length and in degree of equalization throughout the π-framework. It has been suggested[11] that a molecule is aromatic if its C-C bonds are between 1.36 and 1.43 Å in length, and is a polyene if it has alternating bond lengths of 1.34-1.36 Å for the C=C bonds and 1.44-1.48 Å for the C-C bonds. Conformity to the geometric requirements described is a valid criterion for aromaticity, but accurate geometrical information is not always available for a given molecule.

2) Thermodynamical Data as a Criterion for Aromaticity

A low ground state enthalpy can be indicative of aromatic character. However, the evaluation of the thermochemical data with respect to an increased stability of a molecule due to electron delocalization relies on a comparison with the energy of a hypothetical

molecule with a non-delocalized electron organization. The thermochemical data for the hypothetical molecule can only be estimated from data of real systems and the inadequacy of this estimate leads to significant deviations in the resonance energies calculated.

Typical thermodynamic data measured for a compound are the heat of combustion or the heat of hydrogenation. The analysis of the resonance energy of benzene is illustrative of the thermodynamic criteria for aromaticity and the inherent inaccuracy of this method.[12] The heat of hydrogenation of cyclohexene is -28.59 Kcal mol^{-1}, therefore, that of hypothetical cyclohexatriene could be 3 x -28.59 = -85.8 Kcal mol^{-1}. The observed heat of hydrogenation of benzene is -49.8 Kcal mol^{-1} therefore benzene is 36 Kcal mol^{-1} more stable than cyclohexatriene. However, if the sum of three heats of hydrogenation of ethylene (-32.82 Kcal mol^{-1}) is used to obtain a value for cyclohexatriene, then a value of 48.7 Kcal mol^{-1} is obtained for the resonance energy of benzene. The values of the thermochemical data used to calculate resonance energies are very sensitive to the approximations being made, and hence this method does not seem to provide a definitive criterion for aromaticity.

3) Spectroscopic Observations as Criteria for Aromaticity

Various modern spectroscopic techniques, especially nuclear magnetic resonance (NMR) spectroscopy can provide some experimentally observable criteria for aromatic character. The magnetic field a given nucleus experiences consists of the sum of the applied external field H_o and the magnetic fields induced in the molecule by H_o. The induced magnetic fields in the molecule arise from the motion of its electrons

and can be divided into contributions from 1) electrons surrounding the nucleus which is being observed, 2) electrons of neighboring atoms, and 3) electrons which are freely moving within the molecule.[13] Pauling[14] first proposed that the observed diamagnetic anisotropy of cyclic, conjugated hydrocarbons compared to linear olefins was due to π-electron currents induced when a magnetic field was applied perpendicular to the plane of the molecule. A theoretical basis for this concept was established by London.[15] Pople[16] incorporated and extended the "ring-current" model to explain why the chemical shifts of protons in ^{1}H NMR spectra of aromatic molecules were found generally downfield compared to protons of aliphatic olefins. Many examples have shown that 4n + 2 and 4n π-electron systems show different ^{1}H NMR characteristics.[17] A theoretical explanation of this phenomenon was advanced by Pople and Untch[18] and the following conclusions were developed: 1) The magnitude of the ring current is partially reduced by bond alternation and is more sensitive in larger rings, 2) For 4n + 2 systems and n < 7 the diamagnetic ring current increases with ring size and the magnitude of the ring current will decrease with less effective overlap of the π orbitals, 3) For 4n systems the presence of low lying excited states (a mixing of the ground state wave functions with the excited state wave functions) causes a paramagnetic shift and infinite paramagnetism is predicted in the absence of bond alternation. Distortion of the molecule to remove the degeneracy of the highest occupied and lowest unoccupied orbitals reduces the paramagnetism to that observed, 4) The effect of an induced diamagnetic ring current on the ^{1}H NMR resonances is to cause downfield

shifts (deshielding) in the region outside the cyclic, conjugated, 4n + 2 π-electron system and upfield shifts (shielding) inside the ring, and 5) The reverse situation occurs for a paramagnetic ring current of cyclic, 4n π-electron systems. Therefore, the observed ^{1}H NMR chemical shifts of certain protons provide an experimental criterion for aromaticity as reflected by the presence of an induced diamagnetic ring current which is due to a delocalized π-electron system.

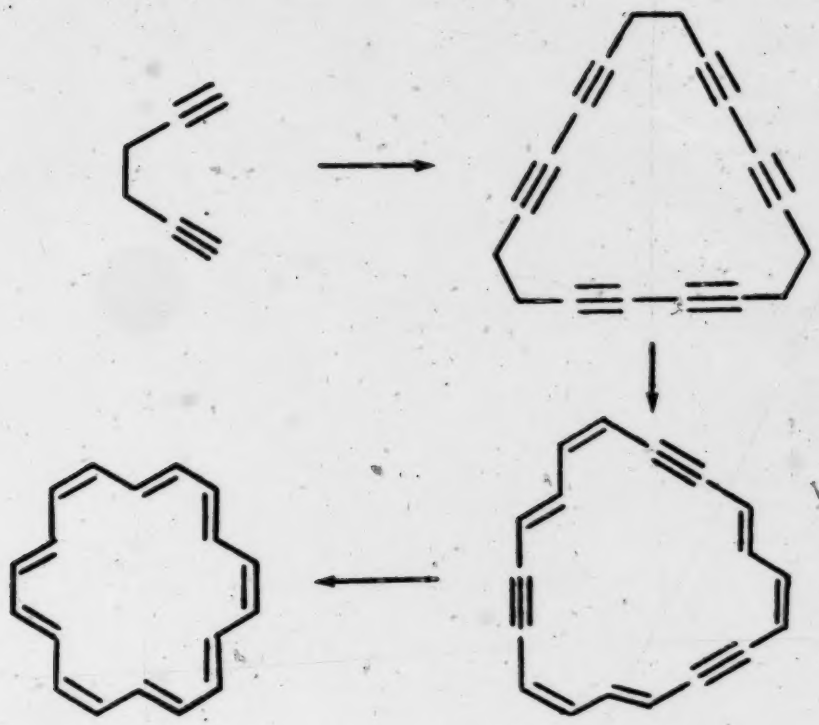
Aromaticity is a concept which describes in a general way the properties of a class of compounds which have an extensively delocalized π-electron system. This concept has survived from the beginnings of organic chemistry and therefore serves some purpose. A compound can be classified in a subjective manner as aromatic based on the observable properties which have been discussed.

C. CYCLIC π-ELECTRON SYSTEMS

Hückel molecular orbital theory (HMO), or more simply, the "4n + 2" rule has guided the synthetic developments in non-benzenoid, aromatic chemistry and has demonstrated remarkable success in predicting the physical properties of cyclic π-electron systems. The HMO theory invokes several approximations which include the following: 1) The π-electron system is separable from the σ-electron system which implies two sets, π and σ, of non-interacting electrons, 2) All of the constituent $2p_z$ electrons in the π-electron system have the same energy, 3) Interaction of non-adjacent $2p_z$ orbitals is negligible, and 4) The molecule consists of equivalent CH units with equal C-C bond lengths.

The HMO theory involves a linear combination of atomic orbitals which produce a set of molecular orbitals (MO), some with lower energy (bonding) and some with higher energy (antibonding) than the original atomic orbitals. It is found that 4n + 2 electrons are required to fill all of the bonding MO's to give a "filled shell" configuration. Hückel stated his 4n + 2 rule as follows:[7] "those monocyclic coplanar systems of trigonally hybridized atoms which contain 4n + 2 electrons will possess relative electronic stability." The HMO theory or the derived "4n + 2" rule has motivated extensive efforts in both theoretical[19] and synthetic organic chemistry.

Cyclooctatetraene was synthesized in 1911 and described as non-aromatic in agreement with HMO predictions.[20] The synthesis of [18]annulene in 1959 by Sondheimer and coworkers[21] represented a major breakthrough in providing synthetic access to monocyclic π-electron systems. The annulenes are fully conjugated, monocyclic polyenes with the number of CH moieties in the ring indicated by an arabic numeral in brackets.[22] The oxidative coupling of linear α,ω-diacetylenes forms macrocyclic polyacetylenes which rearrange by treatment with strong bases to fully conjugated dehydroannulenes which are then partially hydrogenated to annulenes. Annulenes ranging from [12] to [26]annulene have been synthesized[23] and their properties are consistent with HMO theory. The synthesis of [18]annulene is schematically shown as follows.



^{1}H NMR studies of the annulenes provide experimental evidence for induced ring currents in π-electron systems which are consistent with theory, as was previously discussed. Some of the experimental results are summarized in Table 1.

A series of conformationally stable didehydro[4n + 2]annulenes covering a range of 14π- to 30π-electron systems has been synthesized and studied by Nakagawa and coworkers.[28] A study of the effect of ring size on the π-electron system was carried out and it was found that the difference of ^{1}H NMR chemical shifts between outer and inner protons progressively decreased with increasing ring size. These results are summarized in Table 2.

More recent theoretical calculations predicted that annulenes

Table 1. Induced Ring Currents in Annulenes

A. Diamagnetic Ring Current, (4n + 2)π-Electron Systems

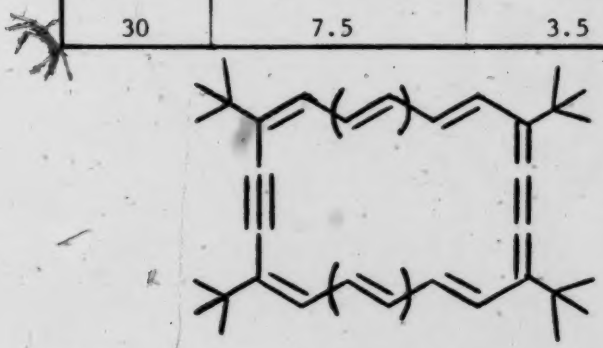
annulene	reference	temperature °C	observed chemical shift, δ from TMS	
			outer protons	inner protons
14	24	-60	7.6	0.0
18	24	-60	9.28	-2.99
22	25	-60	8.5 - 9.1 9.3 - 9.65	-0.4 - -1.2

B. Paramagnetic Ring Current, 4nπ-Electron Systems

16	26	-110	5.4	10.43
24	27	-80	4.73	11.2 - 12.9

Table 2. Induced Diamagnetic Ring Current in Tetra-*tert*-butyldidehydro-[4n + 2]annulenes.[28]

[4n + 2]	observed chemical shift, δ from TMS	
	outer protons	inner protons
14	9.32	-4.44
18	9.87	-3.42
22	9.16	-0.83
26	8.23	1.95
30	7.5	3.5



consisting of a planar skeleton with $(4n + 2)\pi$-electrons would show an induced diamagnetic ring current up to and including [22]annulene.[29] Monodehydro[26]annulene has been prepared and at -90°C the ^1H NMR spectrum (δ from TMS) shows multiplets at 6.2-7.9 and 4.0-4.2.[30] Also, the ^1H NMR spectrum (δ from TMS) of tetra-*tert*-butyldidehydro-[30]annulene at -60°C shows multiplets centered at 7.5 and 3.5.[28] Therefore, the difference in chemical shifts between inner and outer protons indicates that a diamagnetic ring current is sustained even in these large π-electron systems, in contradiction to the theoretical prediction.

Several monocyclic $(4n + 2)\pi$-electron systems carrying a formal charge have been prepared and their properties are consistent with HMO predictions. Some examples of these systems are shown in Figure 1.

By the late 1960's many annulene systems were known except for two noticeable gaps, that of [4] and [10]annulenes. Cyclobutadiene, [4]annulene, has been synthesized in recent years and characterized utilizing low temperature matrix isolation techniques.[37] Several stable derivatives have been prepared and their X-ray analysis has been performed.[38] Recently, the ground state geometry of cyclobutadiene has been shown not to be square by elegant infrared analysis of deuterated and non-deuterated cyclobutadiene generated photochemically at low temperature in an inert gas matrix.[39] Most available evidence strongly suggests that cyclobutadiene is a rectangular singlet in the ground state.[40] The properties and proposed geometry of [4]annulene demonstrate that it is not aromatic in accord with HMO predictions.

The Hückel (4n + 2) rule and its association with the concept of

Figure 1. Some Charged $(4n + 2)\pi$-Electron Systems

n	structure	reference
n = 0		31
		32
n = 1		33
		34
n = 2		35
		36

aromaticity has survived well at the hands of the experimentalist who has provided many tests of its predictions. A discussion of the 10π-electron system follows in Chapter 2.

CHAPTER 2

THE 10π-ELECTRON SYSTEM

A. THE MONOCYCLIC 10π-ELECTRON SYSTEM

Many attempts to prepare a [10]annulene were unsuccessful and this compound was concluded to be too unstable to isolate by the conventional techniques of organic chemistry.[41] The monocyclic [10]-annulene system can have several possible isomeric structures but only three, 4, 5, and 6 are sterically feasible. If $(cis)^5$-[10]annulene 4

4

5

6

acquires a planar conformation, bond angles of 144° are expected, which would generate a severe amount of angle strain and increased van der Waals repulsions between adjacent hydrogen atoms. The interesting question presented by this system was whether the energy gain by electron delocalization would overcome the conformational strain and produce an aromatic 10π-electron system or whether the molecule preferred a non-planar conformation and hence behaved as a cyclic polyene. The *trans*,$(cis)^4$-[10]annulene 5 would be expected to show only partial conjugation due to angle strain and non-bonded interactions. The isomer *trans*,*cis*,*trans*,$(cis)^2$-[10]annulene 6 has a severe non-bonded interaction between two internal hydrogen atoms. Relief of this unfavorable interaction would cause the system to distort from

coplanarity. A further complication was the available low energy pathway for cyclization of the [10]annulenes to dihydronaphthalenes.[42] After extensive experimentation,[43] photolysis of *cis*-9,10-dihydronaphthalene at -60°C provided evidence for the formation of two isomeric [10]annulenes.[44] Optimization of the photolysis conditions with respect to concentration, temperature, and time of irradiation gave synthetically useful amounts of the two isomeric [10]annulenes. The development of superb techniques for manipulating compounds below -60°C[45] led to the successful isolation of the [10]annulenes. On the basis of ^{1}H and ^{13}C NMR spectra, UV spectra and the products resulting from thermolysis, the structures 4 and 5 were assigned.[46]

The properties of these [10]annulenes are summarized as follows. The ^{1}H and ^{13}C NMR spectra of 4 in tetrahydrofuran-d_8 exhibited singlets at δ 5.67 and 130.4 ppm respectively from TMS. Both spectra remained temperature independent over the range of -40°C to -160°C. The UV spectrum of 4 closely resembled that of (*cis*)^{4}-cyclononatetraene.[47] Thermolysis of 4 gave a quantitative yield of *cis*-9,10-dihydronaphthalene. The ^{1}H NMR spectra (tetrahydrofuran-d_8, δ from TMS) of 5 were temperature dependent, exhibiting a sharp singlet at 5.86 at -40°C which separated into two signals at -100°C. The ^{13}C NMR spectrum (tetrahydrofuran-d_8, ppm from TMS) showed one signal (131.2) at -40°C and five signals (128.4, 131.5, 131.6, 132.3, and 132.5) at -100°C. The UV spectrum of 5 showed intense absorption which reflected overlap of three double bonds. The observed absorptions, λ_{max} nm (log ε) in methanol at -50°C were 257 (4.46), 265 (4.30), and 308 (3.7). Thermolysis of 5 gave *trans*-9,10-dihydronaphthalene quantitatively.

In view of these properties the authors stated[46] "One can now

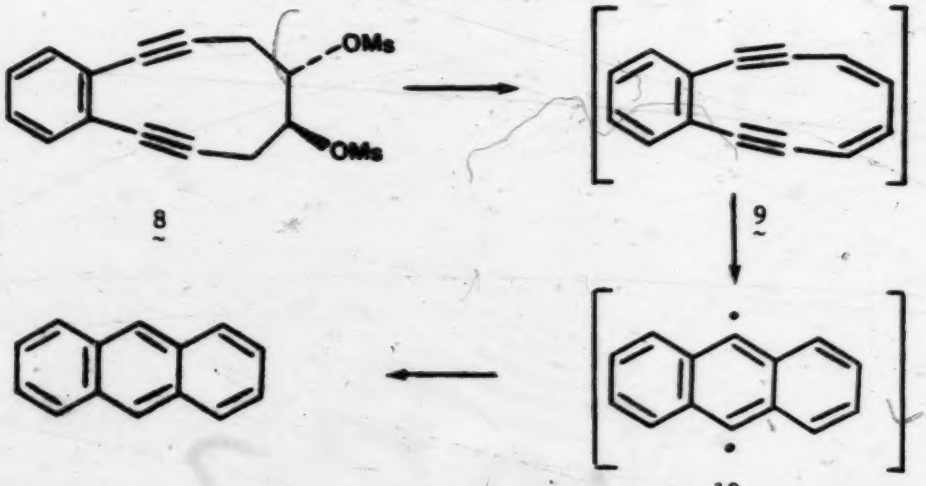
conclude without reservation that the [10]annulenes by no means belong to the category of aromatic compounds."

B. THE 1,5-BISDEHYDRO[10]ANNULENE SYSTEM

The quest for a planar, monocyclic 10π-electron system led to an attempt to prepare 1,5-bisdehydro[10]annulene 7.[48] Sondheimer[49] had demonstrated in [12] and higher annulenes the utility of incorporating acetylenic bonds into a conjugated π-electron system to induce a more rigid and planar configuration. As indicated by Dreiding models, 7 can assume a planar 10π-electron system. Two attempts toward derivatives of 7 are summarized.[48]

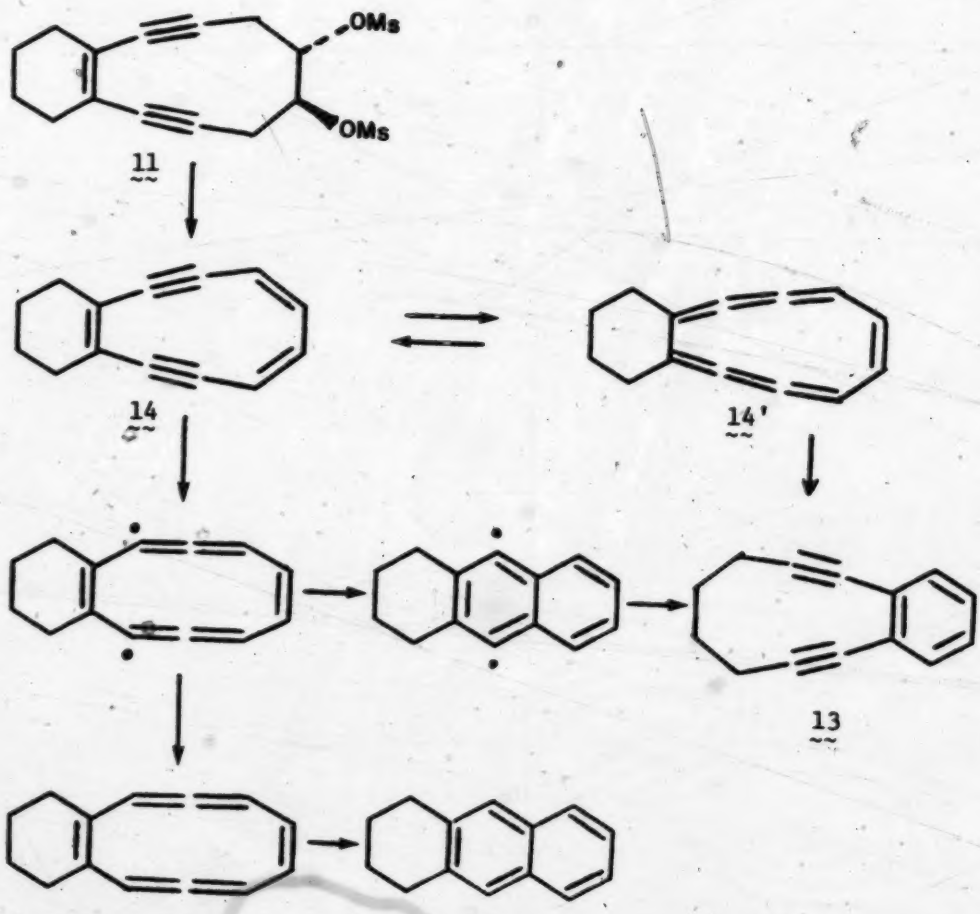
7

When the dimesylate 8 was treated with a variety of bases under various conditions a low yield of anthracene was obtained. The intermediacy of a bisdehydro[10]annulene 9 was postulated and evidence for the formation of the diradical 10 was presented.



8 9 10

Similar base treatment of dimesylate 11 gave tetrahydroanthracene 12. However, a new product 13 was also obtained when 11 was treated with sodium methoxide at -30°C. The formation of 13 could be explained by a "Cope-like" rearrangement of bisdehydro[10]annulene 14. Therefore, if the bisdehydro[10]annulene 14 was formed it is less stable than the benzene derivative 13. These results are summarized in the scheme below. If 14 indeed formed and rearranged to 13, this indicated that the 10π-electron system was less stable than the 6π-electron system of benzene as the ring strain of 14 and 13 were approximately similar.



11

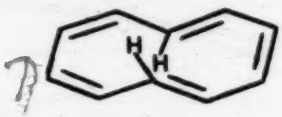
14 ⇌ 14'

13

12

C. THE 1,6-METHANO[10]ANNULENE SYSTEM

A suitable method to test Hückel's rule for a neutral 10π-electron system could involve a modification of *trans,cis,trans,*$(cis)^2$-[10]annulene 6 by replacing the severe steric interaction of the two internal hydrogen atoms with a methylene bridge. Vogel and Roth[50] accomplished the first synthesis of 1,6-methano[10]annulene 15 in 1964. It is generally accepted that 15 represents an aromatic 10π-electron system based on its observed physical properties.[51] The ^1H NMR spectrum (carbon tetrachloride, δ from TMS) of 15 shows a singlet at -0.5 for the methylene protons and a complex multiplet centered at 7.1 for the eight olefinic protons indicating the presence of a diamagnetic ring current. The UV spectrum is consistent with a highly delocalized π-electron system with maxima, λnm (log ε) at 254 (4.90), 298 (3.80), and 360 (2.25). The chemistry of 15 demonstrates a degree of "benzene like" stability, summarized as follows: 1) little tendency to polymerize upon heating, 2) no reaction with maleic anhydride in refluxing benzene, and 3) 15 gives mono- and disubstituted products when treated with electrophilic reagents. An X-ray crystallographic study[52] of the 2-carboxylic acid derivative showed an approximate planar geometry with a distortion of about 20°. The bond lengths of the conjugated π-electron system varied from 1.37 to 1.42 Å consistent with an aromatic system. The distance between C1 and C6 was found to be 2.26 Å.



6

15

Evidence for the existence of a non-negligible 1,6-transannular interaction in 15 seems to be manifested in the ultraviolet[53] and the photoelectron spectra.[54] Theoretical treatments also support the presence of this interaction.[55] Valence tautomerism of several C11 substituted 1,6-methano[10]annulenes (such as 15a and 15b) between the bridged annulene form 15 and the "bisnorcaradiene" form 16 has been demonstrated by variable temperature ^{1}H and ^{13}C NMR spectroscopy.[56] However, no tautomerism has been detected for the parent hydrocarbon 15 and its ^{1}H and ^{13}C NMR spectra are temperature independent[57]. In view of the geometry of 15 and the above observations, it is not unreasonable to expect some electronic interaction between carbons 1 and 6. Therefore, it is possible that 15 may not reflect the true nature of a hypothetical, monocyclic, planar 10π-electron system due to the perturbation caused by a 1,6-transannular bonding interaction.

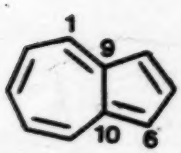
15 $R_1 = R_2 = H$ 16

15a $R_1 = R_2 = CH_3$

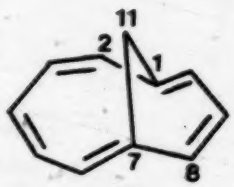
15b $R_1 = CH_3$, $R_2 = CN$

It has been suggested that azulene 17 is a good approximation of a planar 10π-electron system based on HMO calculations[8c] and on the experimental observation that the C9–C10 bond is almost completely σ in character (1.49 Å)[58] which indicates a negligible π-bonding interaction between C9 and C10. This result is in contrast to that of naphthalene 18 which has a calculated C9-C10 π-bond order of 0.518 and an experimental C9-C10 bond length of 1.39 Å.[59]

A better model for a 10π-electron system might be constructed by removing the σ bond in azulene 17 and replacing it with a methylene bridge to give 1,5-methano[10]annulene 19. The synthesis of this novel structure 19 would provide a new model for a monocyclic 10π-electron system. Also, by comparison of its properties with those of 15, an evaluation might be possible of the degree to which the transannular interaction, if it exists, perturbs the monocyclic 10π-electron system of 15.



17



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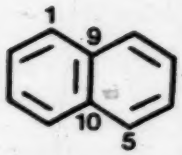


18

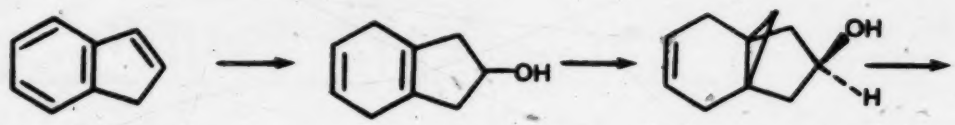
CHAPTER 3

SYNTHETIC APPROACHES TOWARD 1,5-METHANO[10]ANNULENE

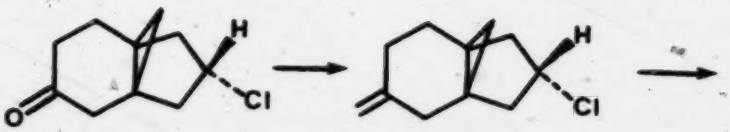
The synthesis of 1,5-methano[10]annulene 19 and a study of its physical properties would provide a more detailed understanding of the 10π-electron system. The interest generated by this compound motivated several attempts toward its synthesis which have been reported and are briefly outlined.

1) R.E. Klem and P Radlick.[60]

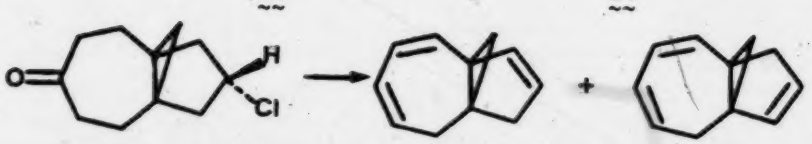
Starting from indene 20, a series of routine steps led to the diene 21. Cyclopropanation[61] to 22 and subsequent functional transformation gave the chloride 23. A Wittig reaction gave the *exo*-methylene compound 24 which was ring expanded[62] to the ketone 25. Subsequent functional changes led to a mixture of isomeric trienes 26 and 27. Further attempts based mainly on dehydrogenation methods failed to give any 1,5-methano[10]annulene 19.



20 21 22



23 24

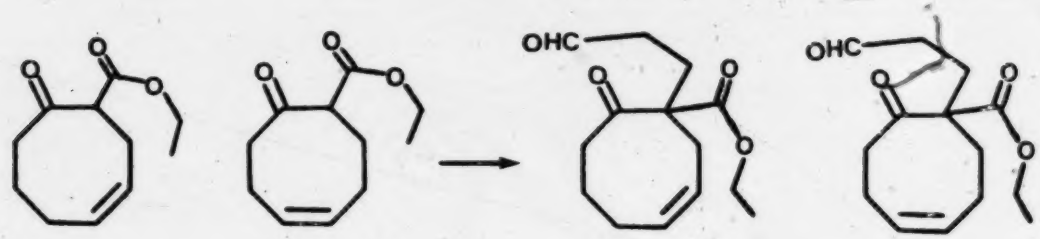


25 26 27

2) B.P.D. Chong and J.R. Wiseman[63]

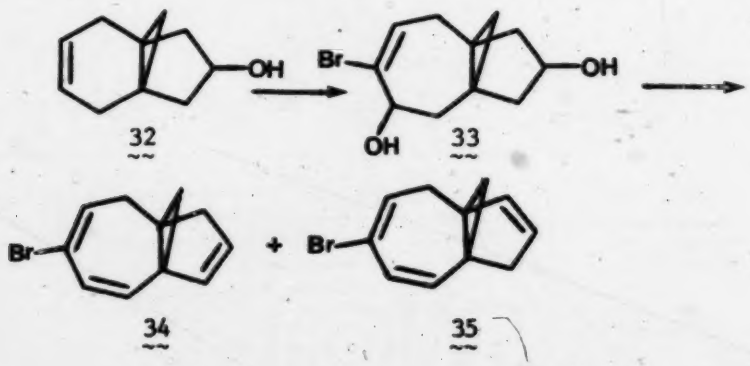
Michael addition of acrolein with a mixture of keto-esters 28

and 29 gave the condensation products 30 and 31. Attempts to cyclize and decarboxylate these aldehydes were unsuccessful.



28 29 30 31

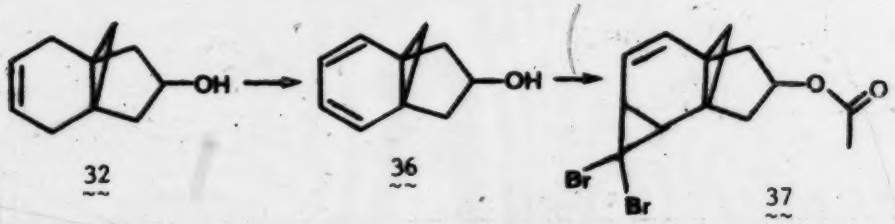
Conversion of 32 by dibromocarbene insertion, silver catalyzed dibromocyclopropane ring opening, and subsequent hydrolysis gave a diol 33. The diol 33 was converted to the corresponding dimesylate which eliminated upon treatment with base to give an isomeric mixture of bromotrienes 34 and 35. Attempts to dehydrogenate these compounds to



32 33 34 35

4-bromo-1,5-methano[10]annulene by several methods failed.

Conversion of 32 by a bromination-dehydrobromination sequence to 36 followed by acetate formation and dibromocarbene insertion gave 37.

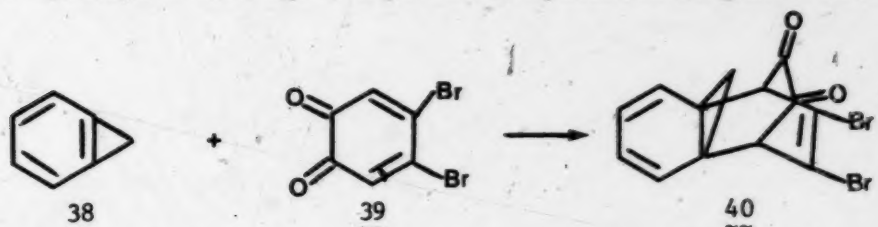


32 36 37

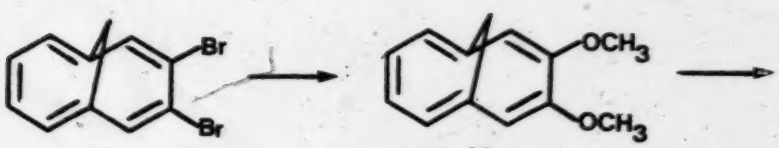
Attempts to open the dibromocyclopropane ring in 37 were unsuccessful.

3) E. Vogel, J. Ippen, and V. Buch[64]

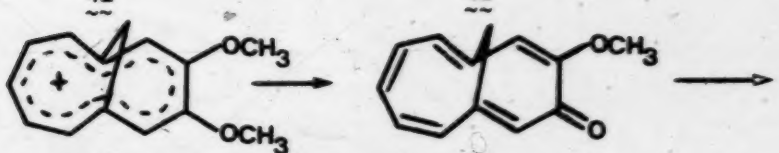
Benzocyclopropene 38 was condensed with 4,5-dibromo-*o*-benzoquinone 39 to give the adduct 40. Irradiation of 40 resulted in decarbonylation to give 41. By a standard method for transforming arylbromides into the corresponding methoxy compound[65] 42 was obtained. Ring expansion of 42 by cuprous chloride catalyzed diazomethane treatment followed directly by hydride abstraction with triphenylmethyl hexafluorophosphate gave a carbenium ion mixture represented by 43 which was hydrolyzed with aqueous potassium hydroxide to give a low yield of



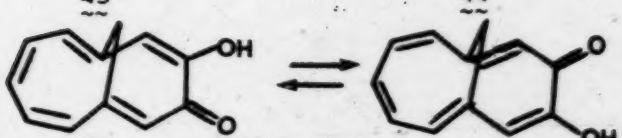
38 39 40



41 42



43 44



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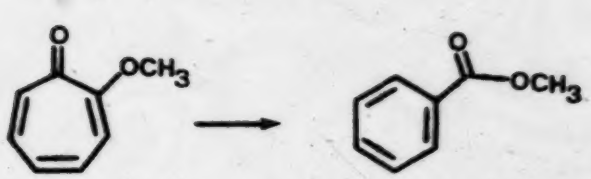
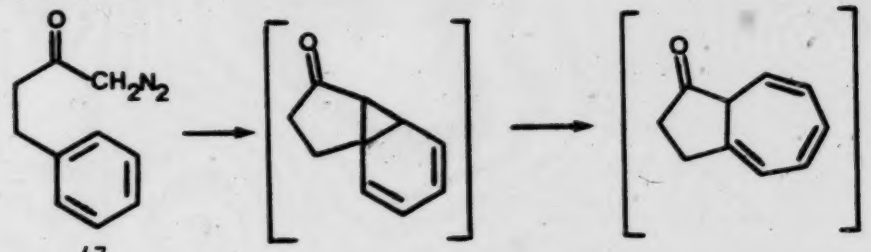


46

44. Heating 44 with aqueous 2N sodium hydroxide followed by acidification gave 45. Attempts to ring contract 44 by heating with bases were unsuccessful. This result was unexpected as the methyl ether of α-tropolone 46 rearranges to methyl benzoate on heating with sodium methoxide in methanol.[66]

4) L. Scott, W.R. Brunsvold, and T.H. Schultz[67]

Copper(I) chloride catalyzed cyclization of diazoketone 47 produced the trienone 48. Selective cyclopropanation of the carbonyl-conjugated olefin in 48 with dimethyloxosulfonium methylide[68] gave 49. Conversion of the ketone 49 by elimination of the corresponding tosylhydrazone[69] gave the triene 50. Treatment with lead tetraacetate provided 51 from which further transformations to a 1,5-methano[10]annulene failed.



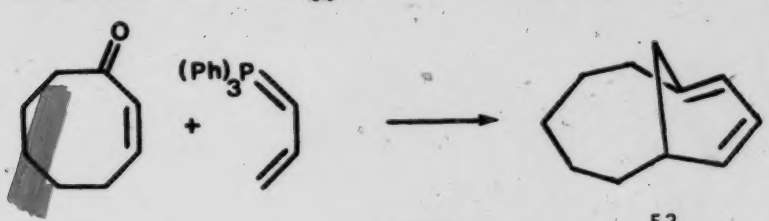
47

48 49

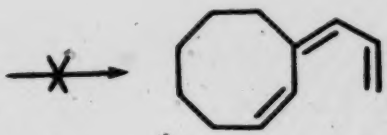
50

51

The numerous synthetic attempts toward 19 did not give any positive clues for its successful preparation, therefore a new approach was investigated. An efficient entry into the correct bicyclo[5.3.1]-undecane skeleton was elegantly solved by Dauben and coworkers.[70] They applied a Michael-Wittig reaction, which was discovered by Büchi and Wüest,[71] for the construction of several strained, bridged olefinic systems. The reaction of cyclooct-1-en-3-one 52 with propylidenetriphenylphosphorane (generated from the corresponding phosphonium bromide and potassium *tert*-butoxide in tetrahydrofuran at room temperature) gave the diene 53 in 63% yield as a stable compound.



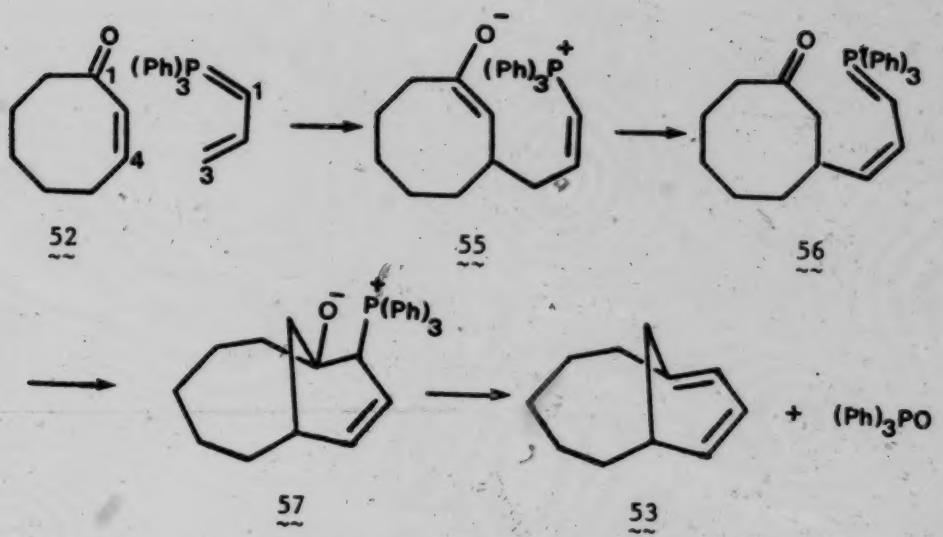
52 53



54

The formation of the 1,2-addition product 54 was not observed.

The mechanism suggested for this reaction[70] involved an initial Michael addition of the terminal C3 position of the phosphorane to the double bond of the α,β-unsaturated ketone 52 to give the intermediate enolate anion 55. Proton abstraction by this enolate regenerates a new phosphorane 56 which condenses intramolecularly to form the betaine 57. The thermodynamic driving force of P-O bond formation and subsequent elimination of triphenylphosphine oxide leads to the introduction of the strained bridgehead double bond.

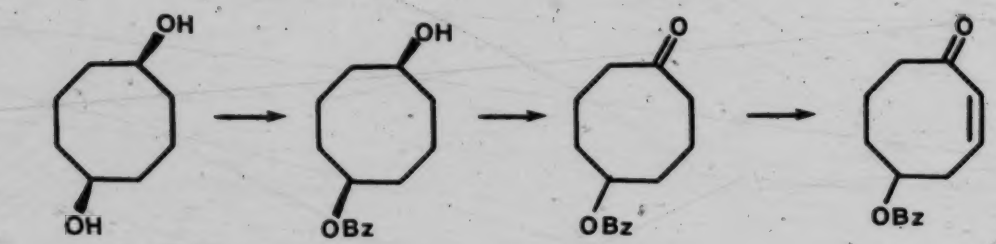


52 55 56 57 53

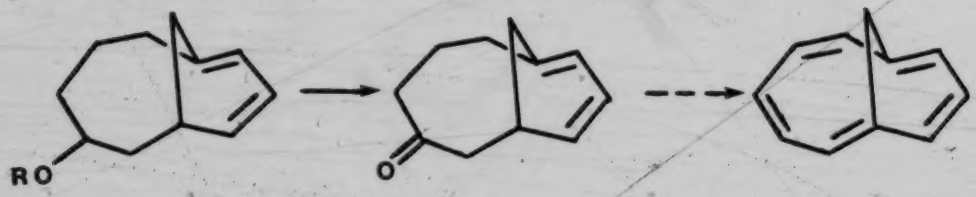
Bicyclo[5.3.1]undeca-7,9-diene 53 was very close to our target 19. In principle, some functionality located in the cyclooctane ring could serve as a means to introduce the remaining unsaturation. The synthetic scheme shown in Figure 2 was attempted.

The readily available *cis*-1,5-cyclooctanediol[72] was monoesterified by treatment with benzoyl chloride in pyridine. Separation from the corresponding dibenzoate and unreacted starting material by chromatography on alumina gave 58 in 60% yield. Oxidation of 58 by the method of Rao and Filler[73] gave the keto-benzoate 59 in 85% yield. The most efficient method to prepare the enone-benzoate 60 was found to be the selenoxide fragmentation reaction.[74] Treatment of 59 in ethyl acetate with phenylselenium chloride gave the corresponding α-selenide which was directly oxidized with hydrogen peroxide in aqueous tetrahydrofuran to give eneone-benzoate 60 in 48% yield.

Figure 2. A Synthetic Approach to 1,5-Methano[10]annulene.



58 59 60



61 R = Bz

62 R = H

63 19

With the functionalized cyclooctenone 60 available, the intramolecular Wittig reaction was performed in a similar manner as reported[70] and the desired condensation product 61 was obtained in 20% yield. Attempts to optimize this reaction were not successful. The benzoate group of 61 was removed with a catalytic amount of sodium methoxide in anhydrous methanol to give the alcohol 62 in 58% yield as a colorless oil. Oxidation of 62 by Collin's method[77] gave the ketone 63 in 64% yield.

The structures 58 to 63 were assigned on the basis of their spectral data (see experimental). The ^1H NMR spectrum ($CDCl_3$, δ from TMS) of 63 showed the following features: 1) a doublet of doublets at 2.02, $J_{11a,b}$ = 10 Hz, $J_{11,7}$ = 4.0 Hz, due to one of the bridge methylene protons, 2) a broad singlet at 2.22 consisting of seven protons, 3) a multiplet centered at 2.40 due to one proton, 4) a multiplet centered at 2.64 due to two protons, 5) the olefinic pattern showed a broad doublet at 5.60, J = 4.0 Hz, due to one proton and a multiplet centered at 6.05 consisting of two protons. The ir spectrum (CCl_4) showed a carbonyl absorption at 1710 cm^{-1}. The ^{13}C NMR spectrum was consistent with the structural assignment. The mass spectrum was also consistent, m/e calculated for $C_{11}H_{14}O$ = 162.1045, observed 162.1042.

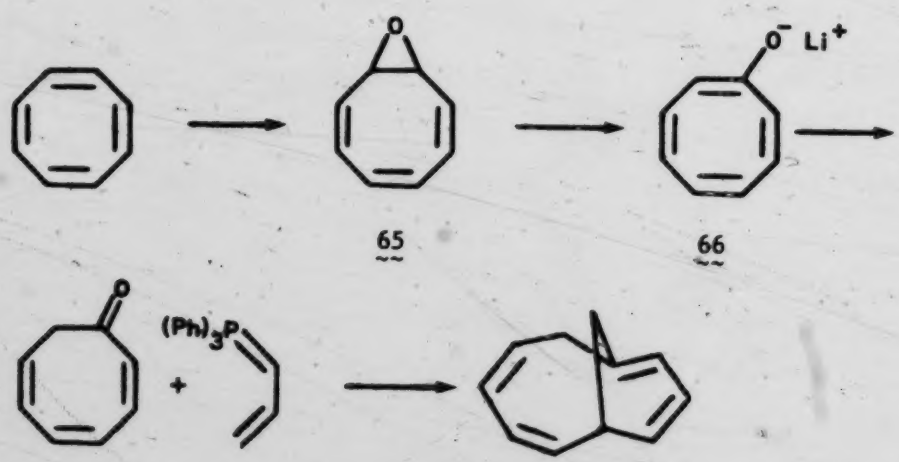
Attempts to further functionalize the ketone 63 by the selenoxide fragmentation reaction led to a complex mixture of products.[76] This route was not pursued any further due to the success of an alternate pathway which is described in the next chapter.

CHAPTER 4

THE CONSTRUCTION OF THE 1,5-METHANO[10]ANNULENE SKELETON

It was evident that the Michael-Wittig cyclization was an efficient entry into the bicyclo[5.3.1]undecane system and showed promise as the key step toward the synthesis of the 1,5-methano[10]-annulene skeleton. If a greater degree of unsaturation was introduced before the Wittig reaction, the difficulties encountered in the previous attempt might by circumvented. A good candidate to test this premise was cycloocta-2,4,6-trienone 64 which was readily available.[77]

Preparation of 64 was performed by a slightly modified procedure of that reported by Cope.[77] Monoepoxidation of cyclooctatetraene[78] with *meta*-chloroperbenzoic acid gave 65 in 60% yield. Treatment of epoxide 65 with lithium diisopropylamide at -40°C led to the lithium enolate 66 which was protonated to give 64 in 88% yield. The spectral data of 64 (see experimental) were consistent with those reported by Cope.



65 66

64 67 68

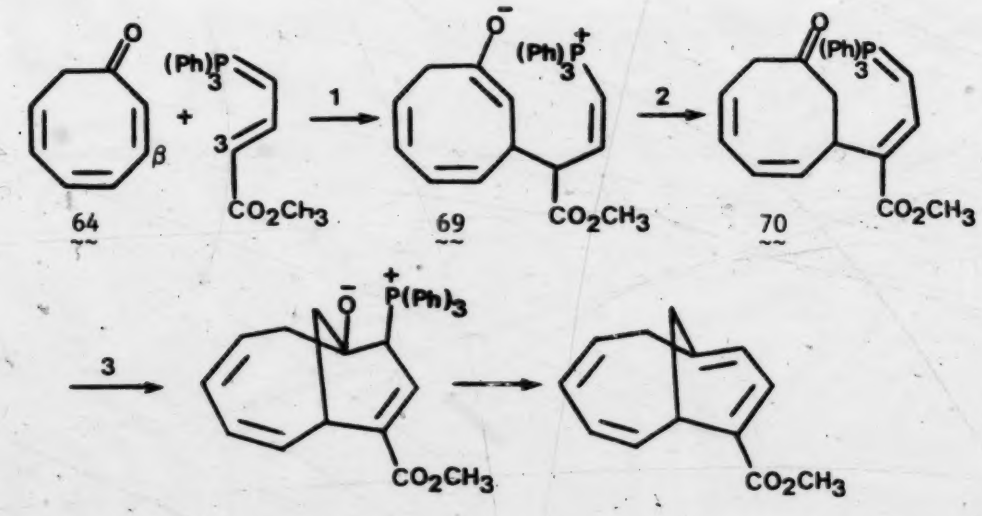
Several attempts to execute the Michael-Wittig cyclization between 64 and propylidenetriphenylphosphorane 67 gave very low yields (6%) of the desired product bicyclo[5.3.1]undeca-2,4,7,9-tetraene 68 as a colorless oil and large amounts of unidentifiable polymeric material. Performing the reaction in refluxing tetrahydrofuran rather than at room temperature gave no desired product 68. Further attempts to optimize this reaction gave no better result.

The assignment of the structure of the tetraene 68 was based on its spectral data and the expected manner of formation. The ^{1}H NMR spectra ($CDCl_3$, δ from TMS) showed the following features: 1) a broad doublet at 2.08, J = 14.0 Hz, and a doublet at 2.55, J = 14.0 Hz, which were assigned to the bridge methylene protons, 2) a multiplet at 2.75 was assigned to the bridgehead proton H1, 3) a broad singlet at 3.02 consisting of two protons was assigned to the C6 methylene group, and 4) a broad doublet at 5.06, J = 12.0 Hz of one proton and a complex multiplet 5.4 - 6.2 consisting of six protons was due to the olefinic protons. The above assignments were consistent with proton decoupling experiments. The ^{13}C NMR spectra ($CDCl_3$, ppm from TMS) was in accord with the proposed structure and is schematically shown in Figure 26. The mass spectrum was consistent, m/e calculated for $C_{11}H_{12}$ = 144.0930, observed 144.0930.

Exploratory attempts to dehydrogenate 68 with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) to 1,5-methano[10]annulene 19 did not show any promise for success.[79]

It was hoped that the Michael-Wittig cyclization of the trienone 64 could be improved by changing the properties of the ylide.

As previously mentioned, the condensation can be visualized as proceeding through three consecutive steps: 1) the initial Michael addition of the ylide to trienone 64 to form the zwitterion intermediate 69, 2) the proton transfer to produce the ylide 70, and 3) the ring closure via a Wittig reaction. By introducing a carbomethoxy group at



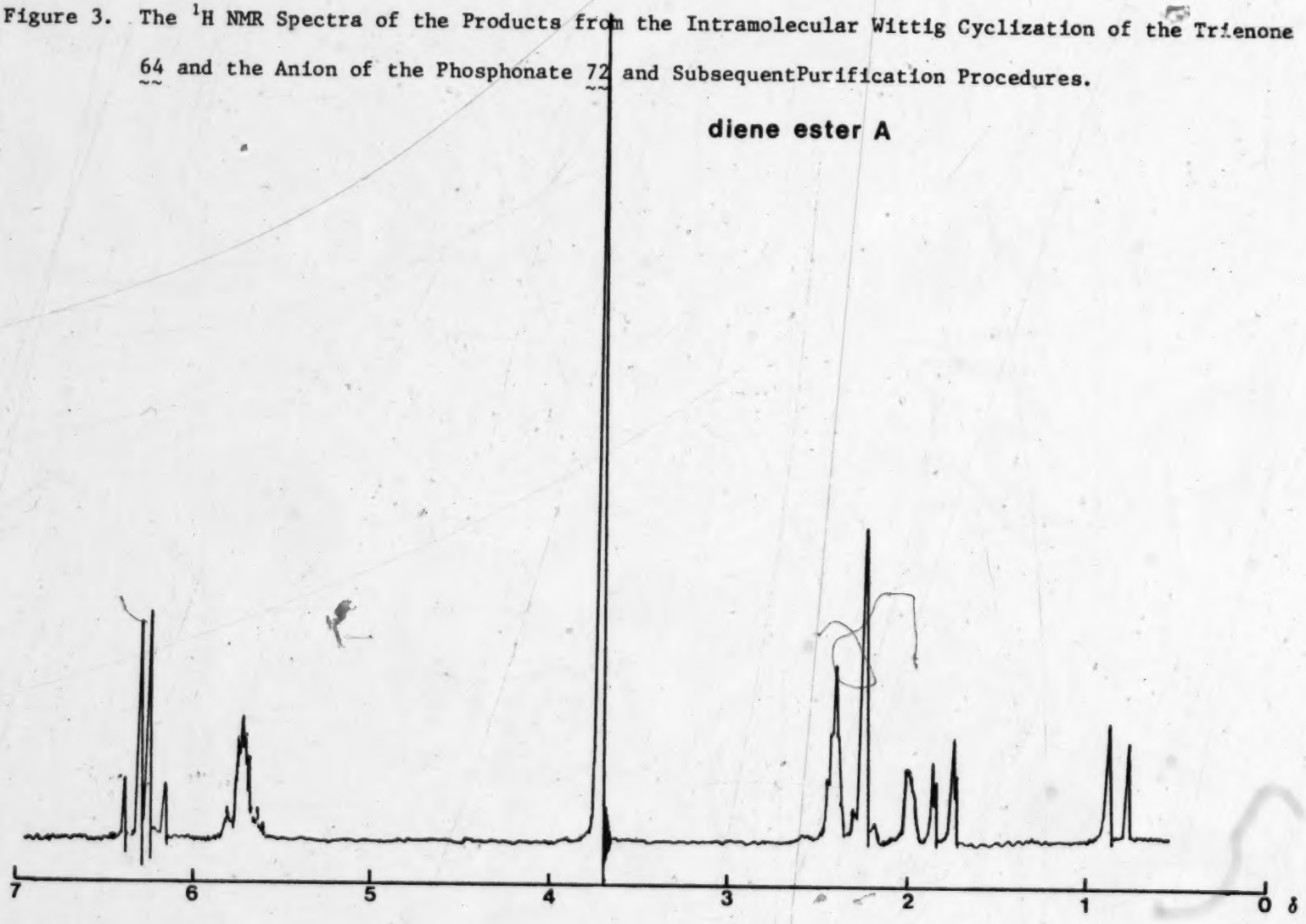
C3 of the phosphorane, it was hoped that the nucleophilicity of the C3 center of the ylide toward the β-carbon of the enone system of 64 would be enhanced, and also the rate of proton transfer in the ensuing step might be facilitated. The use of phosphonate carbanions was also considered because of the documented success of this Wadsworth-Emmons modification[80] of the Wittig reaction, especially in cases where ketones fail to react with stabilized phosphoranes. Both the stabilized phosphorane 71 and the phosphonate 72 were prepared to test the above hypothesis. Treatment of the trienone 64 with phosphorane 71 over

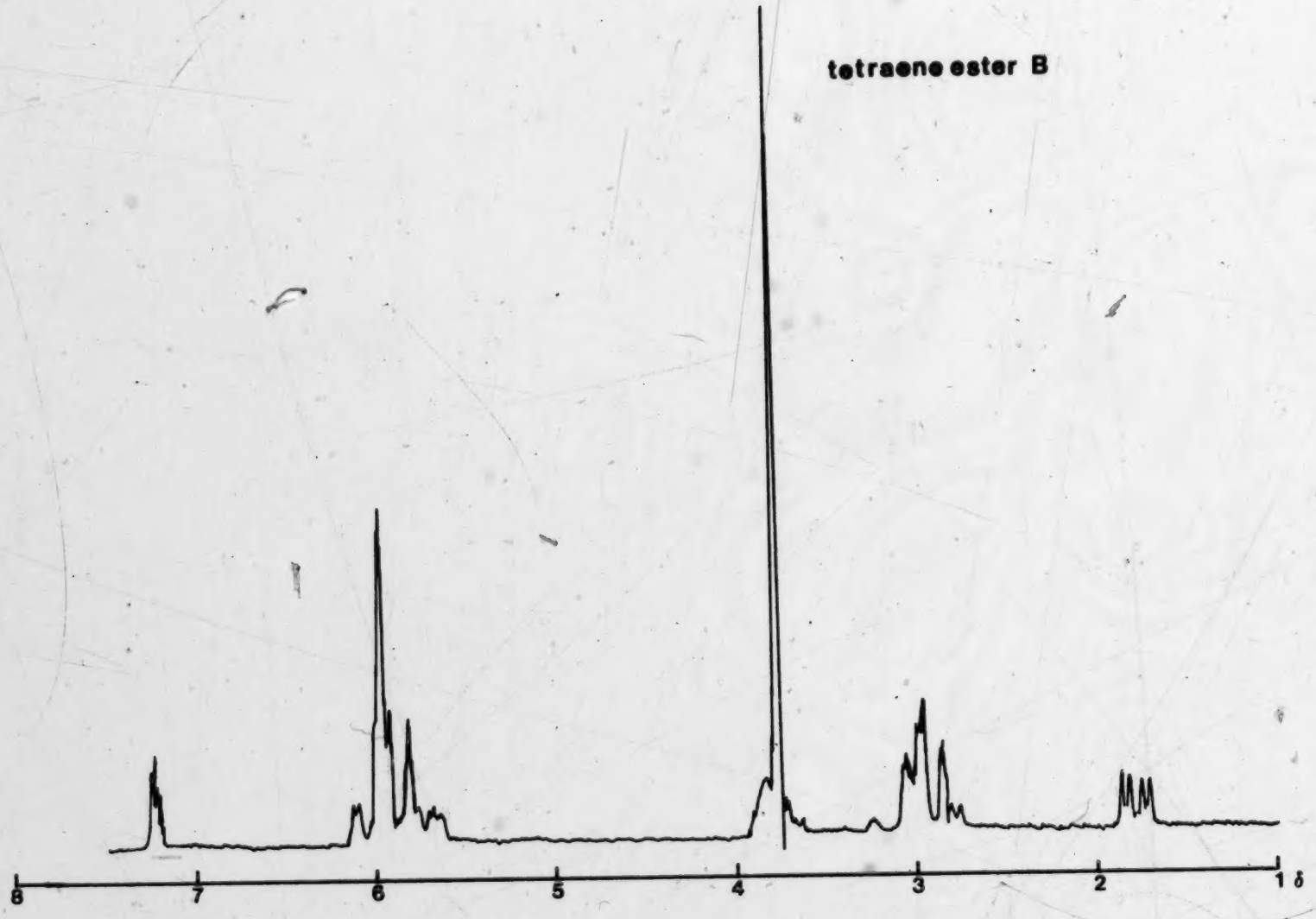
several days at room temperature gave a poor yield (about 5%) of the desired tetraene ester product 73 (see below for its structural assignment).[79]

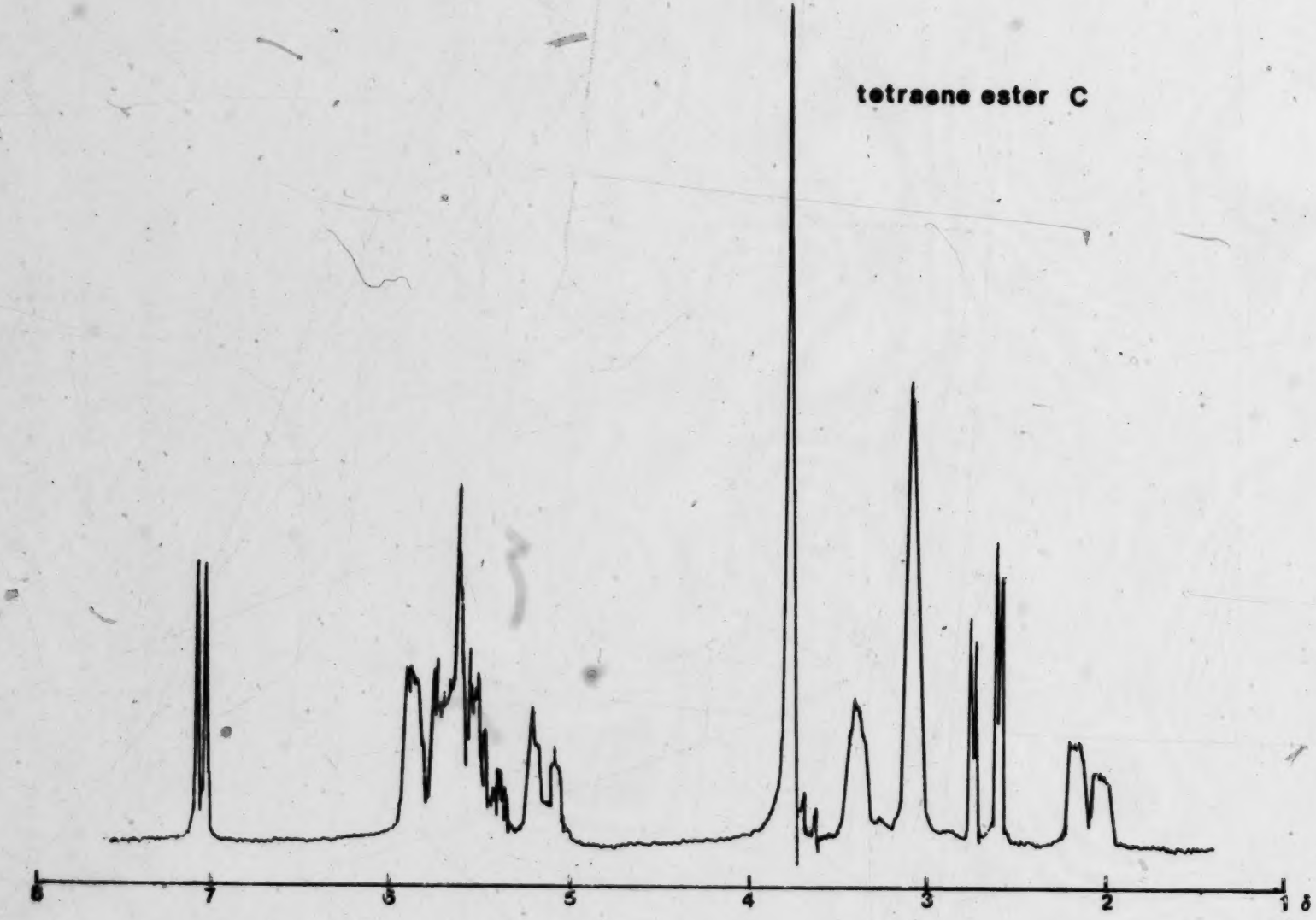
Condensation of the trienone 64 with the anion of methyl 4-(dimethylphosphinyl)-2-butenoate 72 gave what appeared to be a mixture of tetraene esters in 25% yield. The ^{1}H NMR spectrum of the mixture was difficult to analyse. Coupled gc-mass spectral analysis of the mixture showed that it consisted of two isomeric products with a molecular weight of 202. Application of preparative gas chromatography with an SE-30 column at 225°C resulted in the isolation of the observed peaks. Analysis of the ^{1}H NMR spectrum indicated that the compound with the shorter retention time was a diene ester A and the other was a tetraene ester B. Separation of the isomeric mixture could also be accomplished by preparative thin layer chromatography (ptlc) with 10% $AgNO_3$ impregnated silica gel with hexane. ^{1}H NMR analysis of the faster band (r_f = 0.5) indicated a new tetraene ester C and the other band (r_f = 0.4) was identical to tetraene ester B isolated by gc. The ^{1}H NMR spectra of A, B, and C are shown in Figure 3.

The expected product from the Michael-Wittig cyclization was 73. The ^{1}H NMR spectra for tetraene esters B and C were distinctly different and upon close examination, that of C was consistent with the expected product 73. The ^{1}H NMR spectrum ($CDCl_3$, δ from TMS) was closely similar to the tetraene 68 previously described and showed the following features: 1) a broad doublet at 2.10, J = 14.0 Hz and a doublet of doublets at 2.66, J = 14.0 Hz, J = 2.4 Hz, which were attributed to the bridge methylene, 2) a broad singlet at 3.09 consisting of two protons was assigned to the C6 methylene, 3) a broad multiplet

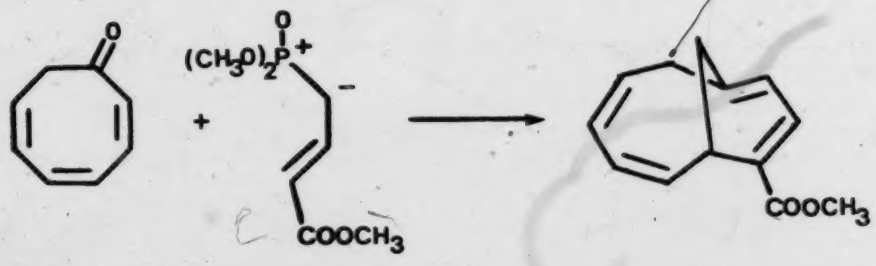
Figure 3. The ^1H NMR Spectra of the Products from the Intramolecular Wittig Cyclization of the Trienone 64 and the Anion of the Phosphonate 72 and Subsequent Purification Procedures.




tetraene ester B
8
7
6
5
4
3
2
1 δ


tetraene ester C
6
7
3
5
4
3
2
1 δ

at 3.40 was assigned to the bridgehead proton, 4) a singlet at 3.77 consisting of three protons was due to the methyl ester, 5) a complex multiplet from 5.0 to 6.0 consisting of five olefinic protons, and 6) a doublet at 7.07, J = 5.0 Hz was assigned to the proton H9. The proton decoupling experiments for 73 are summarized in Figure 4. The ir spectrum (neat) showed absorption due to the ester carbonyl at 1700 cm^{-1} and olefinic absorption at 1575 cm^{-1}. The uv spectrum (cyclohexane) showed λ_{max} nm (log ε) at: 230 (4.01) and 304 (3.74). The ^{13}C NMR spectrum was consistent with the assigned structure and is schematically shown in Figure 26 *. The mass spectrum was consistent, m/e calculated for $C_{13}H_{14}O_2$ = 202.0994, observed 202.0993. The above spectral data provides convincing evidence for the assignment of tetraene ester C as 10-methoxycarbonylbicyclo[5.3.1]undeca-2,4,7,9-tetraene 73.



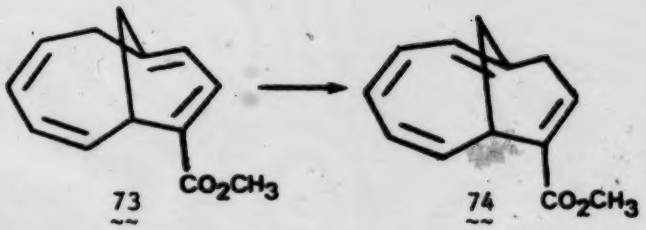
64 72 73

Attention was then directed toward the structure determination of the unexpected tetraene ester B. The 1,10-double bond in 73 is expected to be highly strained as it is located at a bridgehead position.[81] Therefore, an isomerization of this double bond to the 1,2 position to give 74 would relieve some strain by incorporation into a larger ring and this represents a thermodynamically favored process. The

Figure 4. 100 MHz ^{1}H NMR DECOUPLING EXPERIMENTS FOR 73.

Assignment of signals	Blank spectrum	Decoupling frequencies (Hz)					
		209	268	309	340	515	563	589	707
		Observed decoupled signals							
H11	2.10(brd,J=14.0,1)		brs	d, J=14.0				dd J=14.0 J=5.5	
H11	2.66(dd,J=14.0, J=2.4,1)	s		d, J=14.0					
H6	3.09 (brs,2)								
H1	3.40(brs,1)	*	*			*	*		
OCH_3	3.77 (s,3)								
H2	5.14(m,1)			d, J=12.0					
H3,4,5	5.63(m,3)				*	*			
H8	5.89(m,1)	d, J=5.5							brs
H9	7.07(d,J=5.0,1)							s	

*The appearance of the signal is altered compared to the blank



73 74

presence of unreacted phosphonate anion in the condensation reaction could conceivably catalyze this rearrangement at a rate comparable to the formation of 73. The ^{1}H NMR spectrum ($CDCl_3$, δ from TMS) of tetraene ester B was consistent with the proposed structure 74 and showed the following features: 1) a doublet of doublets at 1.75, J = 11.0 Hz, J = 4.0 Hz, was attributed to one of the methylene bridge protons, 2) a complex multiplet centered at 2.98 consisting of three protons, 3) a singlet at 3.77 consisting of three protons due to the methyl ester group and an overlapping broad multiplet centered at 3.84 was assigned to the bridgehead proton H7, 4) a complex multiplet centered at 5.88 consisting of five protons, and 5) a multiplet at 7.22 was assigned to the proton H9. The proton decoupling experiments for 74 are summarized in Figure 5. The composition of the complex multiplet at 2.98 was revealed by simultaneous proton decoupling at 5.89 and 7.22 to consist of one proton of the methylene bridge as a doublet of doublets at 2.88, J = 11.0 Hz, J = 1.5 Hz, and an AB quartet at 2.88 and 3.14, J = 19.0 Hz, due to the C10 methylene protons. The complex multiplet at 5.5 to 6.2 was partially simplified by adding a $CDCl_3$ solution of $Eu(fod)_3$ shift reagent[82] in small increments to the sample. A doublet of doublets, J = 13.0 Hz, J = 4.0 Hz, could be assigned to H6 as it was

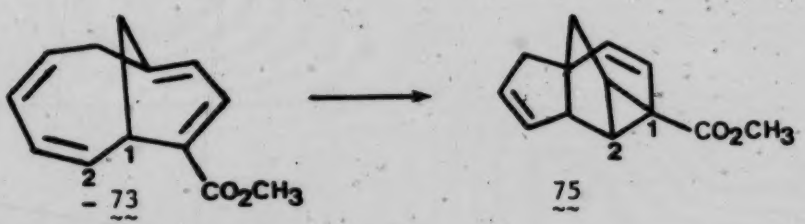
Figure 5. 100 MHz ^{1}H NMR DECOUPLING EXPERIMENTS FOR 74.

Assignment of signals	Blank spectrum	Decoupling Frequencies (Hz)					
		175	295	384	589	722	589 + 722
		Observed decoupling signals					
H11	1.75(dd,J=11.0,J=4.0,1)		*	d, J=11.0			
H11 + two H10	2.98(m,3)	*				*	ABq,J=19.0 + dd, J=11.0, J=1.5
OCH_3	3.77(s,3)	*					
H7	3.84(m,1)						
H2,3,4,5,6	5.88(m,5)						
H9	7.22(m,1)		s				

*The appearance of the signal is altered compared to the blank

shifted downfield clear of the multiplet it was part of originally. The ir spectrum (neat) showed absorption attributed to the ester carbonyl at 1710 cm^{-1} and olefinic absorption at 1630 cm^{-1}. The uv spectrum (cyclohexane) showed λ_{max}^{nm} (log ε) at: 206 (4.39) and 255 (3.32). The ^{13}C NMR spectrum was consistent with the assigned structure and is schematically shown in Figure 26 . The mass spectrum was consistent. m/e calculated for $C_{13}H_{14}O_2$ = 202.0994, observed 202.0987. Therefore the analysis of the spectral data of tetraene ester B is in complete agreement with the assignment of this compound as 8-methoxycarbonyl-bicyclo[5.3.1]undeca-1,3,5,8-tetraene 74.

The remaining piece in the puzzle was the diene ester A. The fact that A was not obtained by ptlc separation and that tetraene ester 73 was not obtained by gc separation of the product mixture suggested that A was likely a thermolysis product of 73. Examination of a molecular model of 73 showed that an intramolecular Diels-Alder type of reaction between the strained diene system of the smaller ring (C7, 8, 9, 10) with the double bond (C2, 3) could be possible. The quadracyclic diene ester 75 predicted from this process was consistent with the

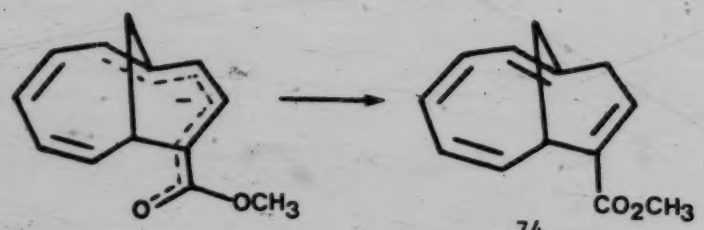


73 75

spectral data of diene ester A. The ^1H NMR spectrum ($CDCl_3$, δ from TMS) showed the following features: 1) a doublet at 0.75, J = 11.0 Hz, consisting of one proton, 2) a doublet of doublets at 1.76, J=11.0 Hz,

J=2.0 Hz, consisting of one proton, 3) a multiplet at 1.94 due to one proton, 4) a multiplet at 2.19 due to two protons, 5) a multiplet at 2.35 due to two protons, 6) a singlet at 3.67 due to the methyl ester group, 7) a multiplet at 5.65 consisting of two olefinic protons, and 8) an AB quartet at 6.18 and 6.30, J = 6.0 Hz consisting of two olefinic protons. The ir spectrum ($CHCl_3$) showed absorption due to the ester at 1725 cm^{-1}. The ^{13}C NMR spectrum was consistent with the structural assignment (see experimental). The mass spectrum was consistent, m/e calculated for $C_{13}H_{14}O_2$ = 202.0994, observed 202.1000. Further confirmation of the proposed thermolytic origin of 75 was obtained by refluxing the tetraene ester 73 in benzene which gave a quantitative yield of 75.

It was desirable to convert 73 into the more thermally stable product 74. This was readily accomplished by treating the isomeric mixture with one equivalent of lithium diisopropylamide at -78°C to give a bright red enolate solution which upon protonation with acetic acid gave only 74 in 95% yield.

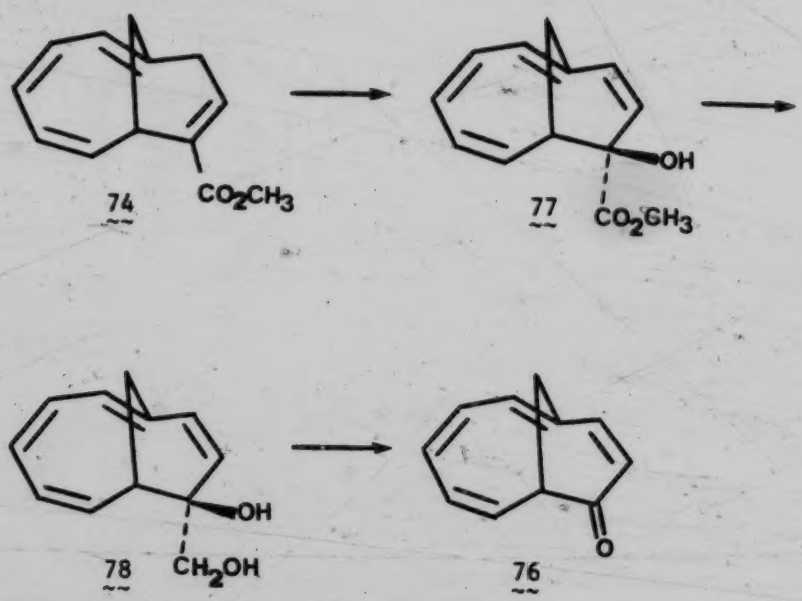


74

The above successful combined Michael-Wittig reaction led to an efficient construction of the bicyclo[5.3.1]undecane ring system containing four carbon-carbon double bonds. The fortuitous olefinic isomerization led to the stable tetraene ester 74. This accomplishment

represented the key step toward the 1,5-methano[10]annulene system.

Further transformations of an α,β-unsaturated ester were then explored. The conversion of 74 into the tetraenone 76 would provide a common precursor for which several methods could be envisioned to prepare 1,5-methano[10]annulene 19. A plausible synthetic scheme for this conversion involves the direct hydroxylation of the enolate anion of 74 to give the hydroxy ester 77 which upon reduction to the diol 78 and subsequent oxidative cleavage would then give the desired tetraenone 76.

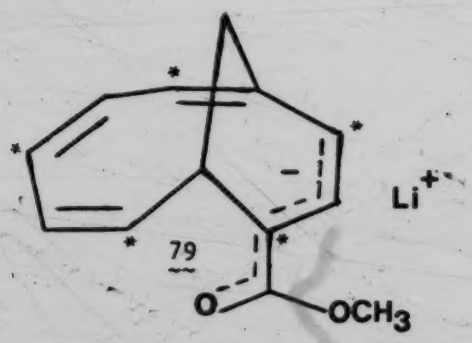


Base catalyzed oxygenation of ketones and esters was a known reaction which gave useful yields for cases having a tertiary α-carbon.[83] This reaction involved bubbling oxygen gas into a solution of the ketone and a strong base such as potassium *tert*-butoxide to form an α-hydroperoxy ketone which was then reduced to the corresponding ketol. A convenient reagent for the reduction step was triethyl phosphite.[84] One-pot hydroxylation could be performed by bubbling oxygen gas into

a solution of the ketone, a strong base, and triethyl phosphite.[85]

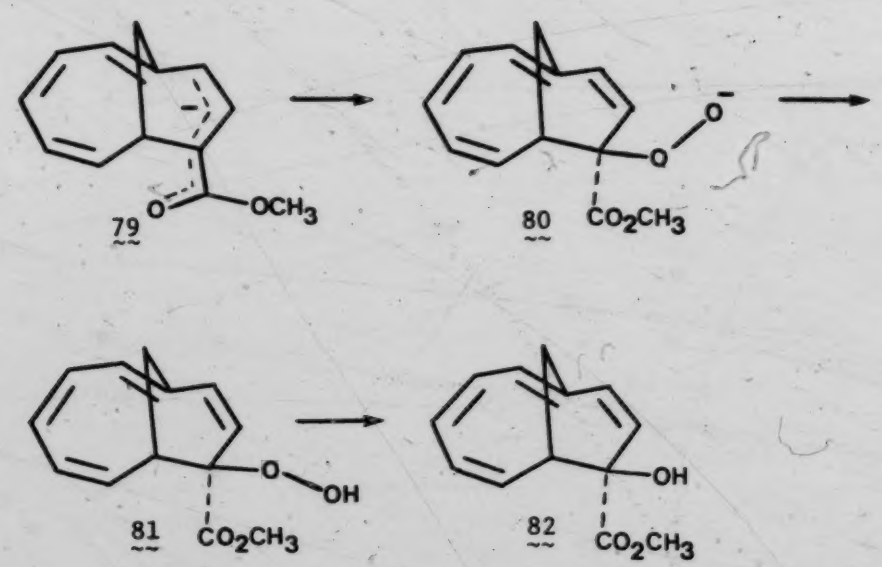
A recent report of oxygenation of the dianion of a carboxylic acid to form α-hydroperoxy acids showed that this reaction proceeded at low temperature (-90°C).[86] Therefore it was highly likely that oxygenation of an ester enolate at -78°C would be successful.

The enolate anion of 74 could form a π-electron delocalized species represented by 79 which has five possible reaction sites (*) with electrophiles. It was observed that protonation of the lithium enolate of 74 with acetic acid took place at only the γ-position of the unsaturated ester system to provide the tetraene ester 74 as the sole product. This result indicated that the extent of π-electron delocalization in 79 may only be limited to the α,β-unsaturated ester system in the small ring. This supposition is supported by molecular models which showed that the 1,2 double bond is distorted out of conjugation from a possible 9,10 double bond due to the σ constraints induced by the methylene bridge. Quenching the lithium enolate of 74 with D_2O also gave 74 with deuterium located only at the C-10 position.



The direct hydroxylation of 74 was carried out by introducing a fine stream of dry oxygen gas through a sintered fritt into a tetrahydrofuran solution at -78°C of the corresponding enolate anion 79

generated from 74 or the isomeric mixture of 73 and 74 with lithium diisopropylamide. The course of this hydroxylation is illustrated for the formation of the desired product 82 as follows. The intermediate hydroperoxy anion 80 was protonated with aqueous 4N HCl and allowed to warm to -40°C. The hydroperoxy ester 81 was not isolated but was reduced directly by the addition of excess triethyl phosphite. Subsequent aqueous workup and purification of the crude product by chromatography on silica gel gave two isomeric hydroxy esters 82 and 83 as approximately a 4:6 mixture in 76% yield.



The structures of the products were readily assigned on the basis of their spectral properties. The ^1H NMR spectrum ($CDCl_3$, δ from TMS) of 82 showed the following features: 1) a broad doublet at 2.43, J = 13.0 Hz due to one proton of the methylene bridge, 2) a multiplet centered at 3.08 consisting of two protons, 3) a singlet at 3.29 due to the hydroxyl proton, 4) a singlet at 3.77 attributed to the methyl ester group, 5) a doublet at 5.38, J = 10.0 Hz was assigned to H10, 6) a multiplet centered at 5.96 consisted of four olefinic protons, and 7)

a doublet at 6.66, J = 10.0 Hz, was assigned to H9. The proton decoupling experiments for 82 are shown in Figure 6. The uv spectrum (cyclohexane) showed λ_{max} nm (log ε) at 200 (4.37 and 288 (3.46). The ir spectrum showed absorptions due to the hydroxyl and ester carbonyl at 3530 and 1730 cm^{-1}, respectively. The ^{13}C NMR spectrum was consistent with the structural assignment and is schematically shown in Figure 26. The mass spectrum was consistent, m/e calculated for $C_{13}H_{14}O_3$ = 218.0943, observed 218.0946.

The ^{1}H NMR spectrum ($CDCl_3$, δ from TMS) of 83 showed the following features: 1) a doublet of doublets at 2.24, J = 11.5 Hz, J = 4.5 Hz, which was assigned to one of the methylene bridge protons, 2) a singlet at 2.41 due to the hydroxyl proton, 3) a doublet of doublets at 2.88, J = 11.5 Hz, J = 1.0 Hz, which was assigned to the other methylene bridge proton, 4) a singlet at 3.78 due to the methyl ester group, 5) a multiplet at 3.84 which was assigned to the bridgehead proton H7, 6) a doublet at 4.58, J = 5.0 Hz, was attributed to H10, 7) a multiplet at 5.86 consisting of five olefinic protons, 8) a doublet of doublets at 7.18, J = 5.0 Hz, J = 1.0 Hz, was attributed to H9. The proton decoupling experiments for 83 are summarized in Figure 7. The uv spectrum (cyclohexane) showed λ_{max} nm (log ε) at: 204 (4.23) and a shoulder at 278 (3.03). The ir spectrum showed absorptions due to the hydroxyl and ester carbonyl at: 3600, 3420, and 1720 cm^{-1}, respectively. The ^{13}C NMR spectrum was consistent with the structural assignment and is schematically shown in Figure 26. The mass spectrum was consistent, m/e calculated for $C_{13}H_{14}O_3$ = 218.0943, observed 218.0941.

The stereochemistry of the hydroxyl group was assigned as *exo*

Figure 6. 100 MHz ^{1}H NMR DECOUPLING EXPERIMENTS FOR 82

Assignment of signals	Blank spectrum	Decoupled frequencies (Hz) 238	312	540	668
		Observed decoupled signals			
H11	2.43(brd,J=13.0,1)		brs	dd, J=13.0 J=4.0	
H7 + H11	3.08(m,2)	brs			dd, J=13.0 J=3.0
OH	3.29(s,1)				brs
OCH_3	3.77(s,3)				
H10	5.38(d,J=10.0,1)				s
H2,3,4,5	5.96(m,4)				
H9	6.66(d,J=10.0,1)	*		s	

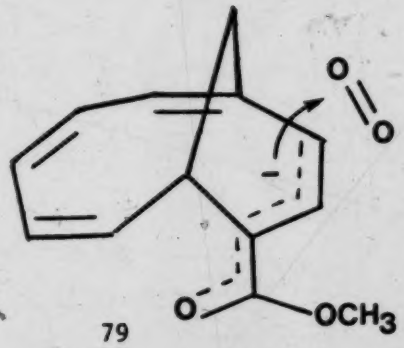
*The appearance of the signal is altered compared to the blank

Figure 7. 100 MHz ^{1}H NMR DECOUPLING EXPERIMENTS FOR 83

Assignment of signals	Blank spectrum	Decoupling frequencies (Hz)					
		222	291	384	460	594	717
		Observed decoupled signals					
H11	2.24(dd,J=11.5,J=4.5,1)		s	d, J=12.0		*	
OH	2.41(s,1)						
H11	2.88(dd,J=11.5,J=1.0,1)	s		d, J=12.0	dd, J=12.0 J=2.0		
OCH_3	3.78(s,3)						
H7	3.84(m,1)						
H10	4.58(d,J=5.0,1)						s
H2,3,4,5,6	5.86(m,s)				*		
H9	7.18(dd,J=5.0,J=1.0,1)				d, J=1.0		

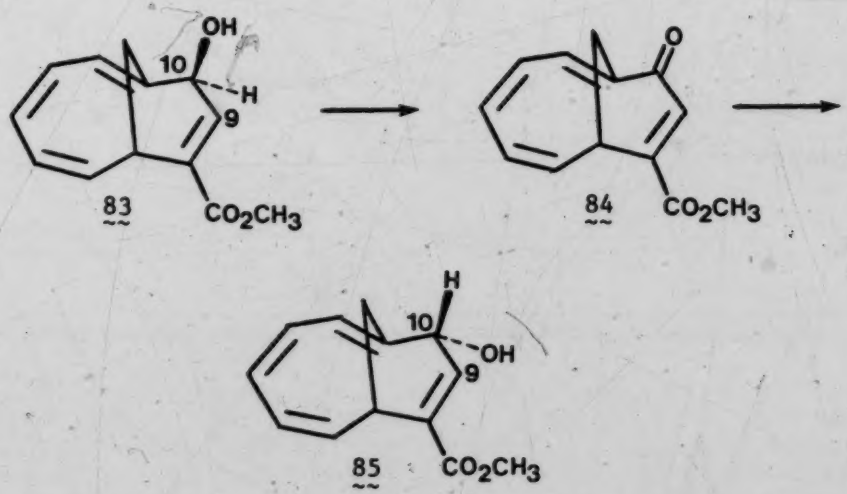
*The appearance of the signal is altered compared to the blank

in both cases on the basis of the preferred approach of the electrophile (O_2) on the assumed bent conformation of the enolate anion 79 as shown by molecular models.



79

Further evidence for this assigned stereochemistry was provided when the 10-hydroxy ester 83 was oxidized with activated manganese dioxide[87] in pentane to the keto-ester 84 followed by reduction with sodium borohydride to give the epimeric hydroxyester 85. Comparison of the size of the spin-spin coupling between H9 and H10 and the respective dihedral angles observed in molecular models was consistent as shown.



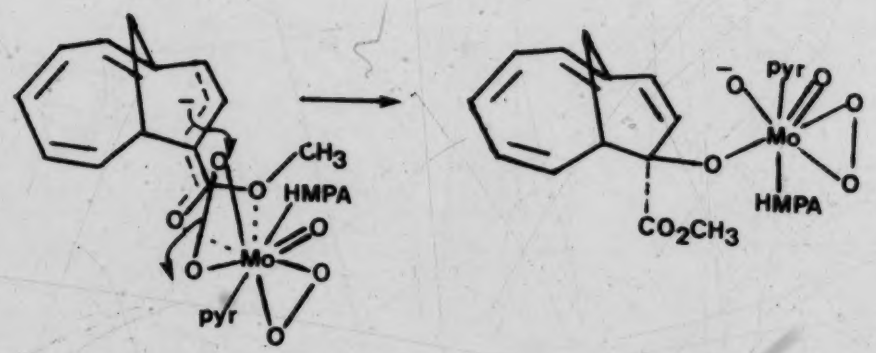
83 84 85

The ^{1}H NMR spectrum of 85 ($CDCl_3$, δ from TMS) showed the following features: 1) a doublet of doublets at 1.92, J = 12.0 Hz, J = 4.0 Hz, which was due to one of the methylene bridge protons, 2) a broad singlet at 2.45 was assigned to the hydroxyl proton, 3) a doublet of doublets at 2.97, J = 12.0 Hz, J = 2.0 Hz, was attributed to the other methylene bridge proton, 4) a singlet at 3.76 contained four protons which were due to the methoxy group and H7, 5) a broad singlet at 4.90 was assigned to H10, 6) a multiplet from 5.6 to 6.2 consisting of five olefinic protons, and 7) a doublet of doublets at 7.02, J = 2.0 Hz, J = 1.0 Hz, was assigned to H9.

	Coupling $J_{9,10}$ (Hz)	Estimated dihedral angle between H9 and H10 from a molecular model
83	5.0	45°
85	2.0	20°

It was gratifying that some α-hydroxylation took place at all in view of the protonation results. However, since the α-hydroxyester 82 was the desired product and it was only available in about 30% yield, another method for effecting direct hydroxylation of an enolate was tried to see if it offered any advantage. Vedejs and coworkers[88] developed a hydroxylation procedure involving the reaction of an enolate anion at low temperature with the transition metal peroxide, oxodiperoxymolybdenum(hexamethylphosphoric triamide)(pyridine) 86 (abbreviated as MoOPH). This method was demonstrated for enolates of ketones,

nitriles, and esters.[89] When this reaction was applied to the enolate anion 79, a 7:3 mixture of hydroxyesters 82 and 83 was obtained in 55% yield after purification and separation by column chromatography on silica gel. The preferential α-addition might be explained as due to coordination of the ester with the transition metal thus directing the electrophilic peroxide ligand to the α position of the enolate as shown.



With the hydroxy ester 82 available, a routine set of reactions provided the ketone 76. The hydroxyester 82 was reduced with lithium aluminum hydride to the diol 78. Oxidative cleavage of the diol 78 with sodium *meta*-periodate in aqueous dioxane gave ketone 76 as a bright yellow crystalline solid after workup, which could be purified by chromatography (silica gel) or by sublimation at 45°C, 0.1 mm.

The structural assignment of the ketone 76 was straightforward from its mode of formation and was consistent with its spectral data. The ^{1}H NMR spectrum ($CDCl_3$, δ from TMS) is shown in Figure 8 and had

the following features: 1) a doublet of doublets at 2.68, J = 12.0 Hz, J = 3.0 Hz, which was due to one of the bridge methylene protons, 2) a multiplet centered at 3.50 consisting of two protons, 3) a doublet at 5.50, J = 10.0 Hz, which was assigned to H9, 4) a multiplet at 6.02 consisting of five olefinic protons, and 5) a broad doublet at 7.38 J = 10.0 Hz, which was assigned to H10. Addition of a carbon tetrachloride solution of $Eu(fod)_3$ shift reagent[82] in increments to a solution of the ketone 76 in carbon tetrachloride led to a simplification of the multiplet centered at 3.5. The bridgehead proton signal was shifted downfield out of this multiplet to reveal itself as a broad singlet and the other bridge methylene proton as a doublet of triplets, J = 12.0 Hz, J = 2.0 Hz, and J = 2.0 Hz. By the relative magnitude of the shift of the two bridge methylene protons upon addition of equal increments of shift reagent it was possible to distinguish these two protons. A plot of the chemical shift versus added shift reagent of the two methylene bridge protons demonstrated a linear relationship as shown in Figure 9. The slope of the plots indicated that the high field signal was shifted more compared to the downfield signal. Since the degree of chemical shift is dependent on the proximity of a given proton to the shift reagent[90] which is complexing in this case at the keto site, the methylene bridge protons could be assigned as shown in Figure 9. The interesting J = 2.0 Hz coupling in the doublet of triplet signal buried in the multiplet centered at 3.50 and assigned as H11b could be due to a long range coupling with the proton H10. This was indeed verified by decoupling experiments in the presence of the shift reagent.

The uv spectrum of 76 (cyclohexane) showed λ_{max} nm (log ε) at

Figure 8. 100 MHz ^{1}H NMR Spectrum of Bicyclo[5.3.1]undeca-1,3,5,9-tetraene-8-one 76

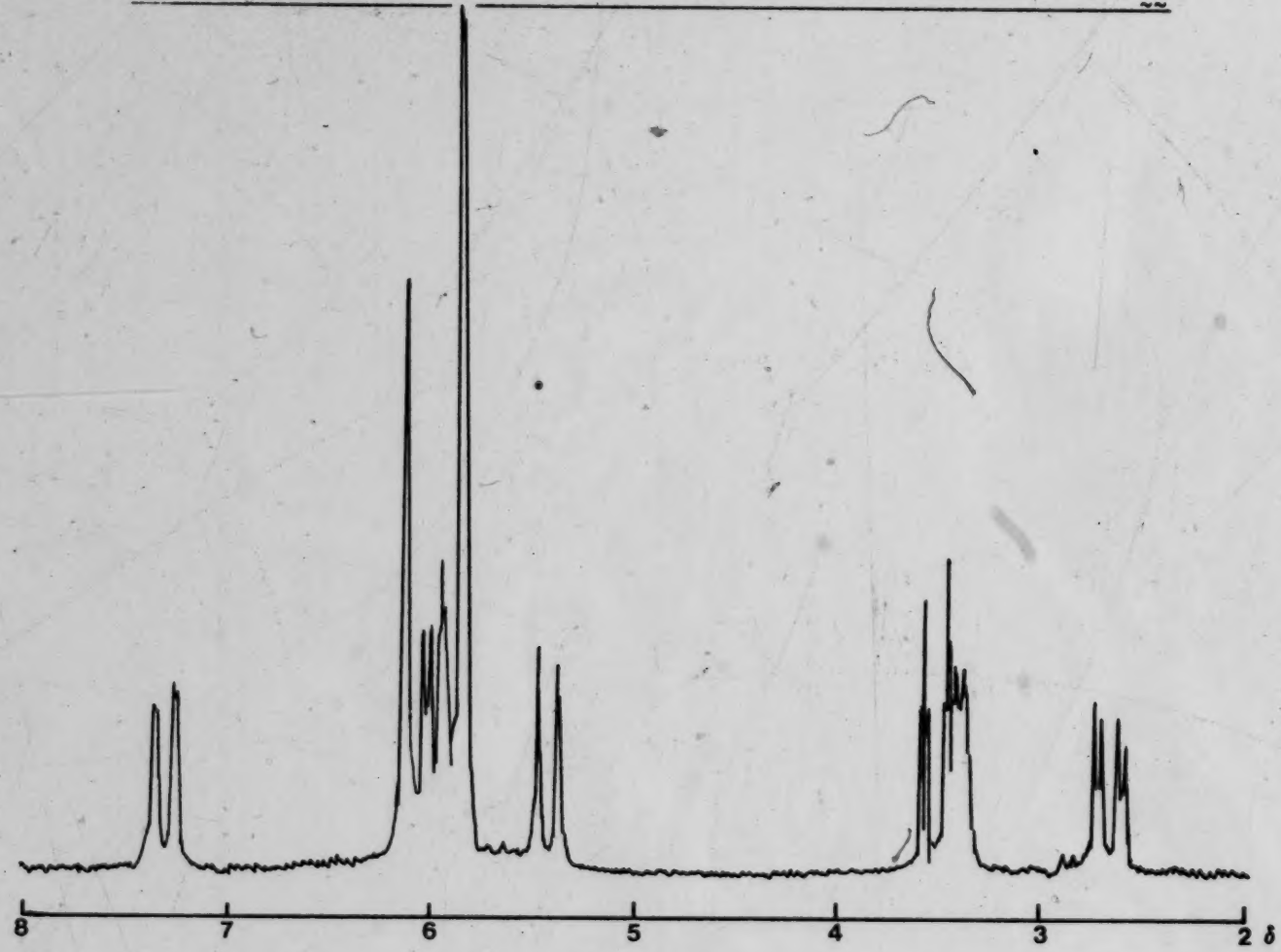
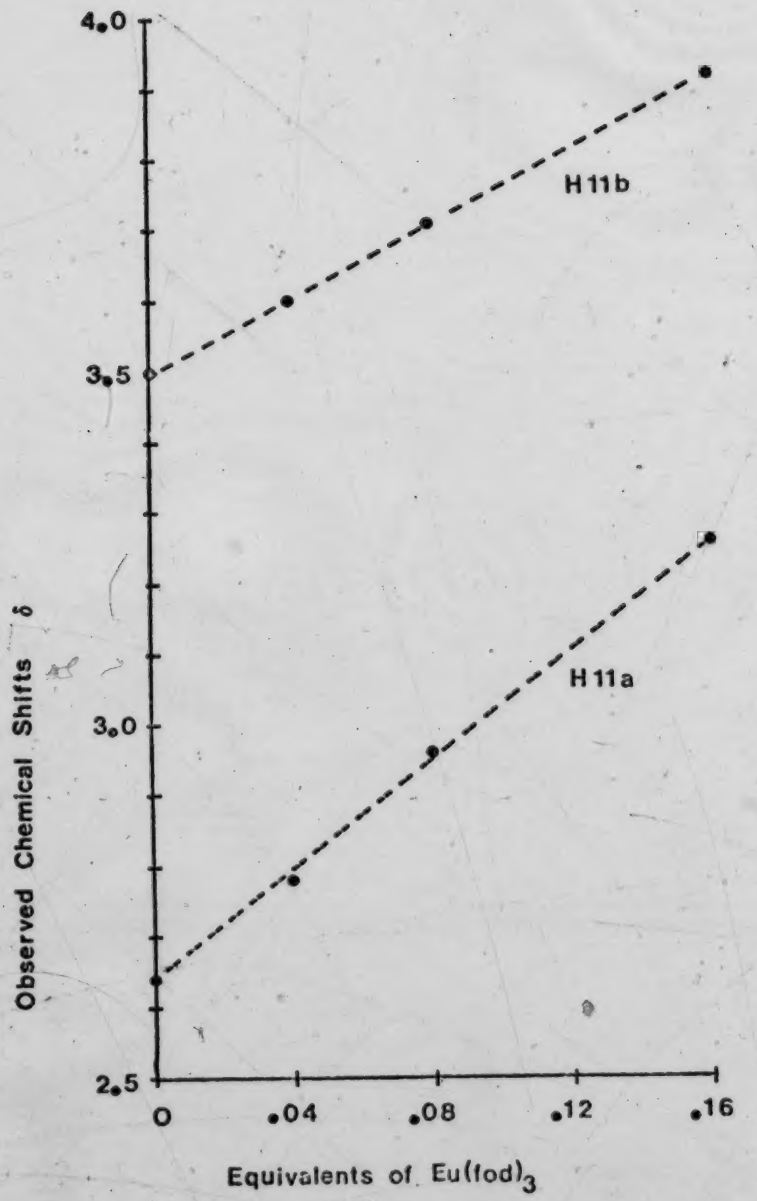
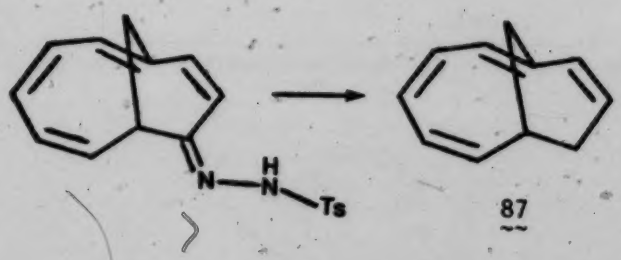


Figure 9. Shift Reagent Study of Bicyclo[5.3.1]undeca-1,3,5,9-tetraene-8-one 76.



220 (4.19), a shoulder at 252 (3.77), 318 (3.46), and a shoulder at 390 (2.41), consistent with an enone system. The ir spectrum showed absorptions due to the ketone at 1660 cm^{-1} and olefinic absorption at 1630 cm^{-1}. The ^{13}C NMR spectrum was consistent with the structural assignment and is schematically shown in Figure 26. The mass spectrum was consistent, m/e calculated for $C_{11}H_{10}O$ = 158.0732, observed 158.0731. A sublimed sample of 76 has a mp of 72-73°C and its combustion analysis (see experimental) was in agreement with the molecular formula.

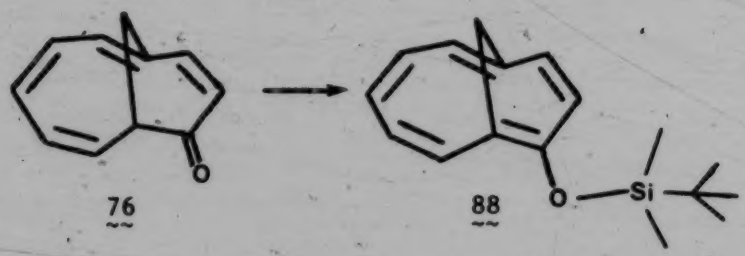
A facile conversion of ketone 76 to 1,5-methano[10]annulene 18 utilizing the olefin synthesis developed by Shapiro and coworkers[91] was conceivable. In this reaction, a ketone containing an α hydrogen is converted to the corresponding tosylhydrazone, which upon treatment with more than two equivalents of an alkyl lithium at room temperature eliminates the tosylhydrazone to give a vinyl anion, which is subsequently protonated to yield the desired olefin. When the tosylhydrazone of ketone 76 was treated with *n*-butyllithium in tetramethylethylenediamine a bright red solution was formed but upon workup only a very small amount of a colorless hydrocarbon product, possibly 87 was isolable. It appeared as if proton abstraction from the bridgehead position was difficult and this attempted reaction was abandoned.[92]



87

The initial failure to obtain the parent 1,5-methano[10]annulene 19 motivated the preparation of some substituted derivatives which were thought to be more synthetically accessible at this time. This would provide important information concerning the physical properites and the kind of synthetic operations that could be performed on this unknown system.

The first example of a 1,5-methano[10]annulene system was prepared by treating the ketone 76 with lithium diisopropylamide at -78°C and trapping the lithium enolate with *tert*-butylchlorodimethylsilane[93] to give the corresponding enol ether 88 as a red oil.



76 88

This compound lost its color when exposed to air (oxygen sensitive), especially when it was neat or highly concentrated.

The ^{1}H NMR spectrum (benzene-d_6, δ from TMS) of 88 shown in Figure 10, exhibited the presence of an induced diamagnetic ring current as reflected by the chemical shifts of the bridge methylene protons at -0.62 as a doublet of doublets, J = 10.0 Hz, J = 2.0 Hz, and at -0.30 as a doublet, J = 10.0 Hz. The two methyl groups on silicon appeared as singlets at 0.21 and 0.32 and the *tert*-butyl group appeared at 1.08. The doublet at 6.20, J = 7.5 Hz was assigned to H9 in view of the electron donating properties of the silyl enol ether group. The other olefinic signals appeared in the "aromatic region" as a multiplet

Figure 10. 100 MHz ^{1}H NMR Spectrum of the Silyl Enol Ether 88.

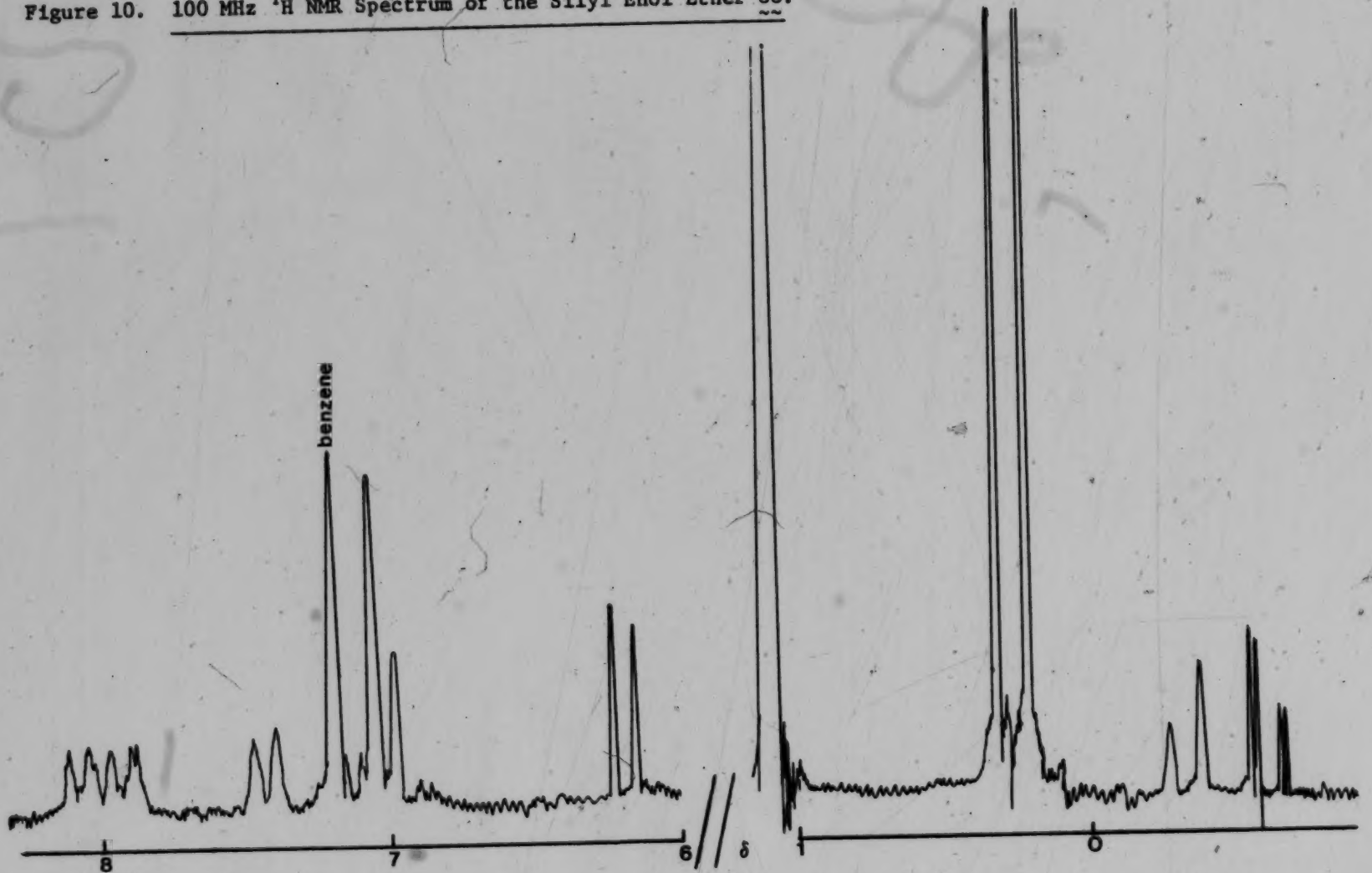


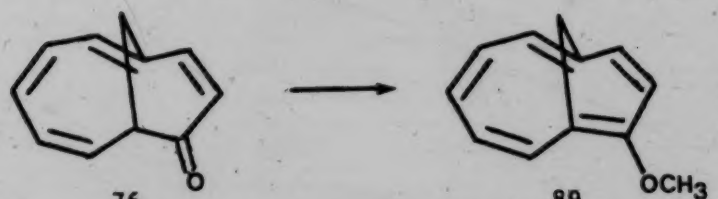
Figure 11. 100 MHz ^{1}H NMR DECOUPLING EXPERIMENTS FOR 88

Assignment of signals	Blank spectrum	Decoupling frequencies (Hz)			
		620	705	743	800
		Observed decoupled signals			
H11	-0.62(dd,J=10.0,J=2.0,1)			d,J=10.0	
H11	-0.30(brd,J=10.0,1)				
$SiCH_3$	0.21(s)				
$SiCH_3$	0.32(s)				
Si-<	1.08(s)				
H9	6.20(d,J=7.5,1)			s	
H3,4,5	7.05(m)				*
H10	7.43(brd,J=7.5,1)	s			
H2	7.93(brd,J=8.0,1)		s	*	
H6	8.07(brd,J=7.5,1)		s		

*The appearance of the signal is altered compared to the blank

centered at 7.05 consisting of three protons and three broad doublets at 7.43, J = 7.5 Hz, 7.93, J = 8.0 Hz, and 8.07, J = 7.5 Hz, each consisting of one proton. Decoupling experiments and an analysis of the spectrum are summarized in Figure 11. The ^{1}H NMR sample of 88 was heated at 120°C for 1 h and the spectrum was again recorded and found to be identical. This particular derivative therefore appeared to be reasonably stable toward thermolysis in the absence of oxygen.

Several other substituted 1,5-methano[10]annulenes were prepared from the ketone 76. O-Alkylation of the sodium enolate of 76 generated in hexamethylphosphoric triamide with sodium hydride at 0°C followed by quenching with methyl fluorosulfonate (Magic Methyl^{TM})[94] gave 8-methoxy-1,5-methano[10]annulene 89 as a red oil. This compound was



76 89

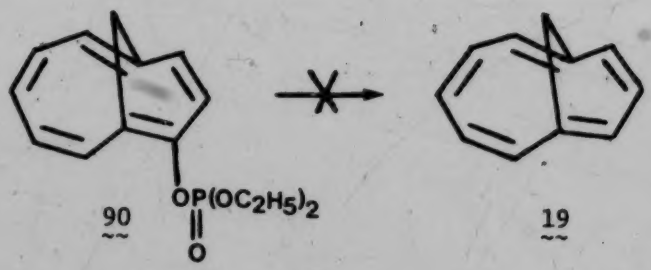
very air sensitive and all operations with it were carried out under an argon atmosphere with careful attention to degassing of the solvents used. Purification was accomplished by chromatography on silica gel (activity V, cyclohexane) with the visible red band being collected to give 89 in 18% yield. The ^{1}H NMR spectrum (acetone-d_6, δ from TMS) showed a high field AB quartet for the methylene bridge protons at -0.34, H11b, and -0.20, H11a, J = 10.0 Hz. The methoxy protons appeared as a singlet at 3.90. The olefinic pattern closely resembled

that of the silyl ether 88 showing the following features: 1) a doublet at 5.85, J = 7.0 Hz, which was assigned to H9, 2) a multiplet centered at 6.95 consisting of three protons due to H3, 4, and 5, 3) a doublet at 7.20, J = 7.0 Hz, which was assigned to H10, 4) a doublet at 7.55, J = 8.0 Hz, was tentatively assigned as H2, and 5) a doublet at 8.06, J = 10.0 Hz, was tentatively assigned as H6. The assignments of H2 and 6 were based on the previous analysis of the ^{1}H NMR spectrum of 88. The uv-visible spectrum with λ_{max}nm (log ε) at 244 (4.0), 290 (4.1), 355 (3.4), and 505 (2.5) showed considerable absorption extending into the visible region and demonstrated a highly delocalized π-electron system. The ^{13}C NMR spectrum was consistent with the assigned structure and is schematically shown in Figure 26. The mass spectrum was consistent, m/e calculated for $C_{12}H_{12}O$ = 172.0888, observed 172.0885. The fragmentation pattern showed major fragments resulting from the loss of H, CH_3, and OCH_3.

Similarly, O-alkylation of the lithium enolate anion of 76 with diethyl chlorophosphate[95] gave the enol phosphate 90 as a red oil which was purified by chromatography on silica gel (activity IV, benzene) to give pure 90 in 90% yield. This compound was relatively easy to handle as it was less oxygen sensitive than the previous derivatives. The ^{1}H NMR spectrum (benzene-d_6, δ from TMS) showed the characteristic high field AB system of the methylene bridge protons as a doublet of doublets at -0.96, J = 10.5 Hz, J = 2.0 Hz and a broad doublet at -0.27, J = 10.5 Hz. The ethoxy groups on phosphorus appeared as a broad triplet at 1.15, J = 7.0 Hz, consisting of six protons and a multiplet at 4.10 consisting of four protons. The olefinic signals showed a similar pattern to those of the enol ether derivatives 88 and 89 with the fol-

lowing features: 1) a doublet at 6.85, J=8.5 Hz, which was assigned to H9, 2) a multiplet centered at 7.03 consisting of three protons, 3) a broad doublet at 7.46, J = 8.5 Hz, which was assigned to H10, and 4) broad doublets at 7.62, J = 6.0 Hz, and 8.60, J = 7.0 Hz, which were tentatively assigned to H2 and H6, respectively.

The main interest in preparing this compound was due to the possibility of cleaving the enol phosphate C-O bond to give 1,5-methano-[10]annulene 19 by the method developed by Ireland and coworkers.[96] Attempts to carry out this reaction did not show any promise for success.[97]



90 19

The physical properties of the three enol ether derivatives 88, 89, and 90 clearly indicate the presence of a diamagnetic ring current in their ^{1}H NMR spectra and showed reasonable stability in the absence of oxygen.

Reaction of ketone 76 with phosphorus pentachloride gave the dichlorotetraene 91 which upon treatment with lithium diisopropyl amide at -78°C in tetrahydrofuran gave a low yield of elimination to 8-chloro-1,5-methano[10]annulene 92. The ^{1}H NMR spectrum (benzene-d_6, δ from TMS) of the crude product showed the high field methylene bridge protons as a doublet of doublets at -0.99, J = 10.0 Hz, J = 2.0 Hz, and a broad

doublet at -0.37, J = 10.0 Hz. The signals due to the olefinic protons were tentatively chosen as a doublet at 6.40, J = 8.0 Hz, a multiplet of three protons centered at 7.0, a broad doublet at 7.27, J = 8.0 Hz, and multiplets at 7.54 and 8.22. Attempted purification by chromatography on silica gel (activity IV, benzene) caused decomposition of the product.

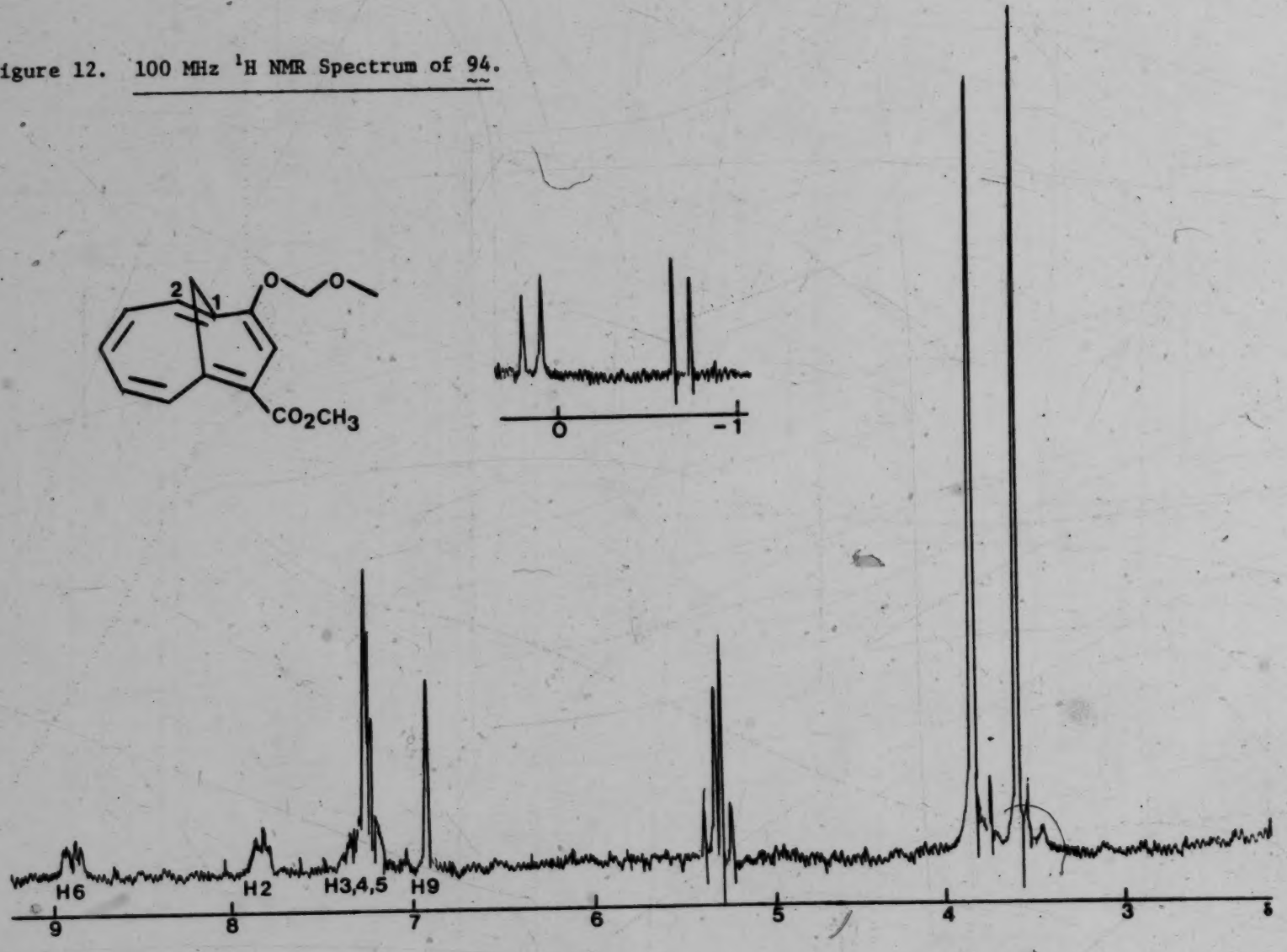
91 92

A set of 8,10-disubstituted 1,5-methano[10]annulene derivatives were prepared from the ketoester 84 available by activated manganese dioxide oxidation of the 10-hydroxyester 83. Treatment of 84 with sodium hydride in hexamethylphosphoric triamide at 0°C gave a bright purple enolate anion which was quenched with methyl fluorosulfonate (Magic Methyl™) to give the methoxyester 93 as a red oil. This disubstituted system was much less sensitive to oxygen than the previous derivatives and lost its color only after several minutes standing neat in the open air. Purification was accomplished by chromatography on silica gel (activity V, cyclohexane) and the visible red band was collected.

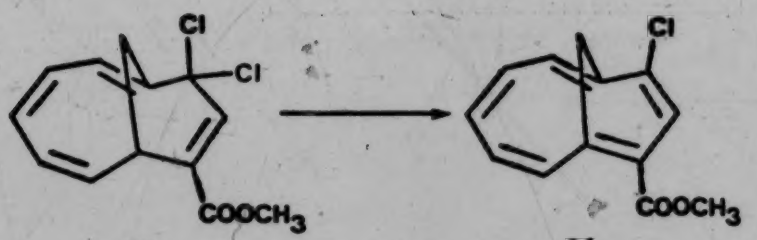
The ^{1}H NMR spectrum (acetone-d_6, δ from TMS) of 93 showed the following features: 1) an AB system consisting of a doublet at -0.41, J = 10.0 Hz, and a doublet at 0.36, J = 10.0 Hz, due to the methylene bridge protons, 2) two singlets at 3.86 and 3.93 due to the methoxy and methoxyester groups, respectively, 3) a singlet at 6.41 which was assigned to H9, 4) a multiplet centered at 7.14 consisting of three protons, and 5) two multiplets at 7.56 and 8.86, each of one proton, which were tentatively assigned as H2 and H6. The ^{13}C NMR spectrum was consistent with the structural assignment and is schematically shown in Figure 26. The uv spectrum showed λ_{max} nm (log ε) at: 248 (4.8), 294 (4.6), 375 (4.1) and a shoulder at 500 (3.1). The mass spectrum was consistent with the assigned structure, m/e calculated for $C_{14}H_{14}O_3$ = 230.0943, observed 230.0934. The fragmentation pattern showed a stable m^+ - H fragment along with the loss of CH_3, OCH_3, and 2 OCH_3.

Similar formation of the sodium enolate anion of 84 and quenching with chloromethyl methyl ether[96] gave the disubstituted derivative 94 as a red oil. This derivative had properties similar to 93. The ^{1}H NMR spectrum ($CDCl_3$, δ from TMS) of 94 with assignments of the signals is shown in Figure 12.

Figure 12. 100 MHz ^{1}H NMR Spectrum of 94.



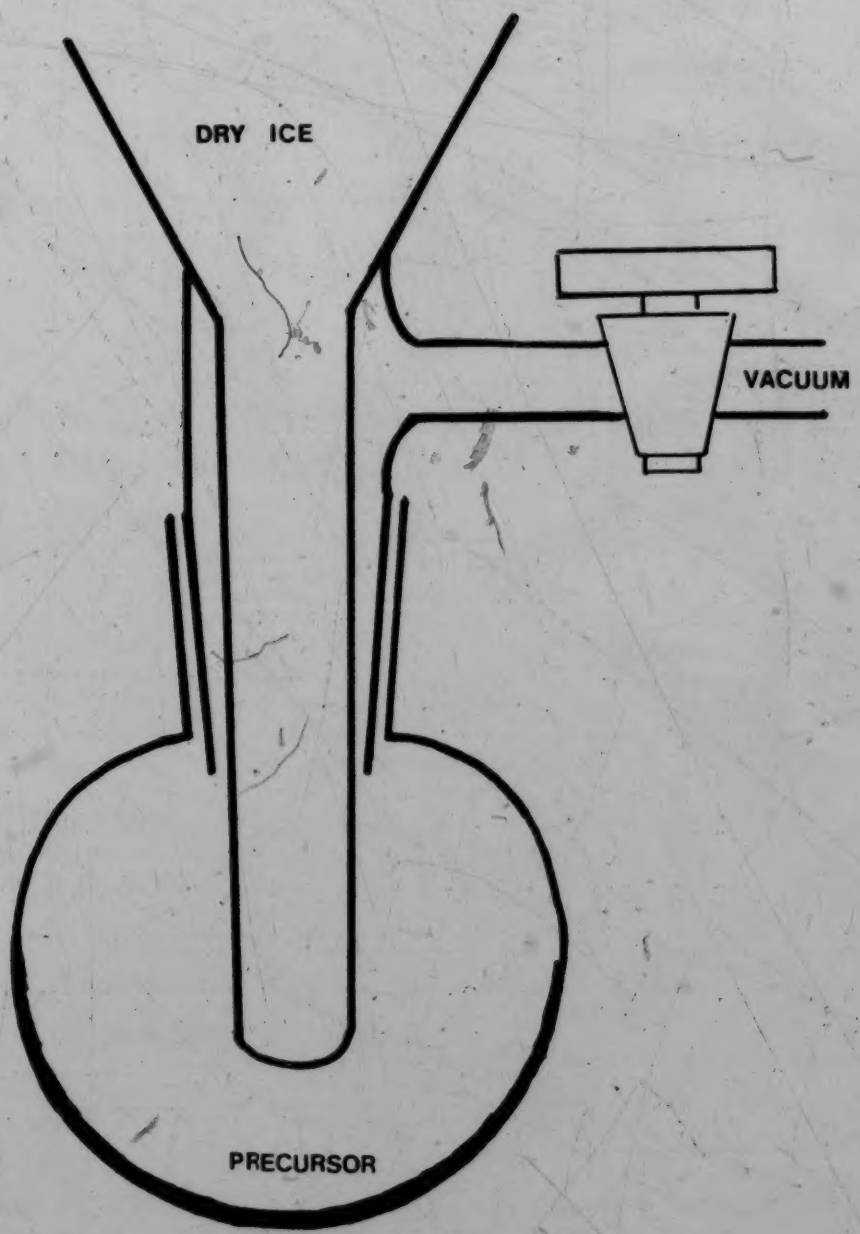
Treatment of ketoester 84 with phosphorus pentachloride gave the dichloro compound 95 which was treated with lithium diisopropylamide at -78°C in tetrahydrofuran to give a crude mixture containing the chloroester 96 as a red oil. From the ^{1}H NMR spectrum (benzene-d_6, δ from TMS) of the crude product the following features could be picked out for 96: 1) a doublet at -1.20, J = 10.5 Hz, and a broad doublet at -0.22, J = 10.5 Hz, due to the methylene bridge protons, 2) a multiplet at 7.00 consisting of three protons, 3) a singlet at 7.54 which could be assigned to H9, and 4) two multiplets at 7.83 and 8.62 each consisting of one proton. Attempted purification by chromatography on silica gel (activity IV, benzene) resulted in decomposition.



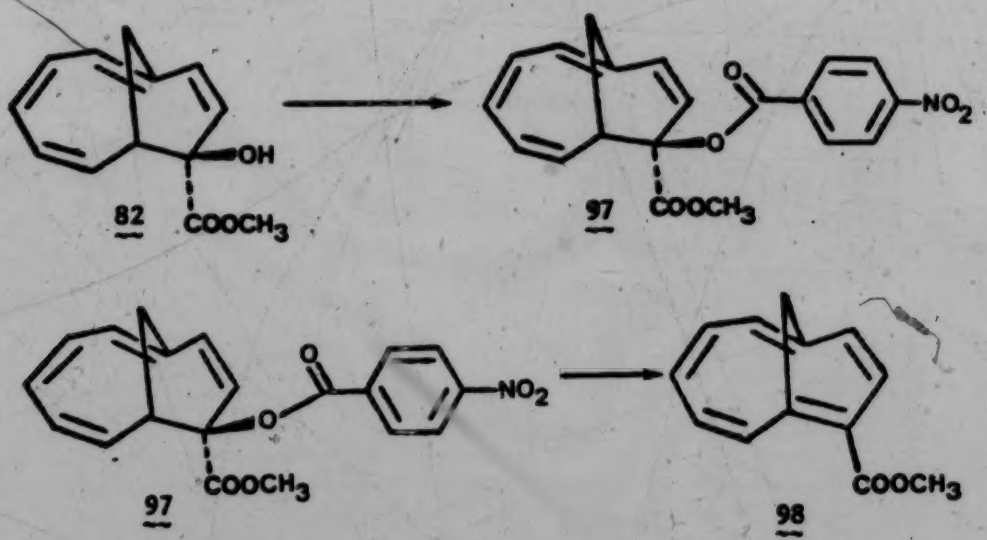
95 96

The possibility of forming the 7,8 double bond of the 1,5-methano-[10]annulene system by a pyrolytic *cis*-elimination could be explored with a suitable precursor derived from the hydroxyester 82. Conversion of 82 into the corresponding *p*-nitrobenzoate 97 proceeded smoothly. A solid phase pyrolysis was carried out with the apparatus shown in Figure 13. A thin film of 97 was deposited on the inner surface of a round-bottomed flask which was fitted with a cold finger (dry ice, acetone, -78°C) and then was evacuated to 10-15 mm pressure. The flask was immersed into an oil bath at 160°C for five min, during which

Figure 13. Pyrolysis Apparatus.



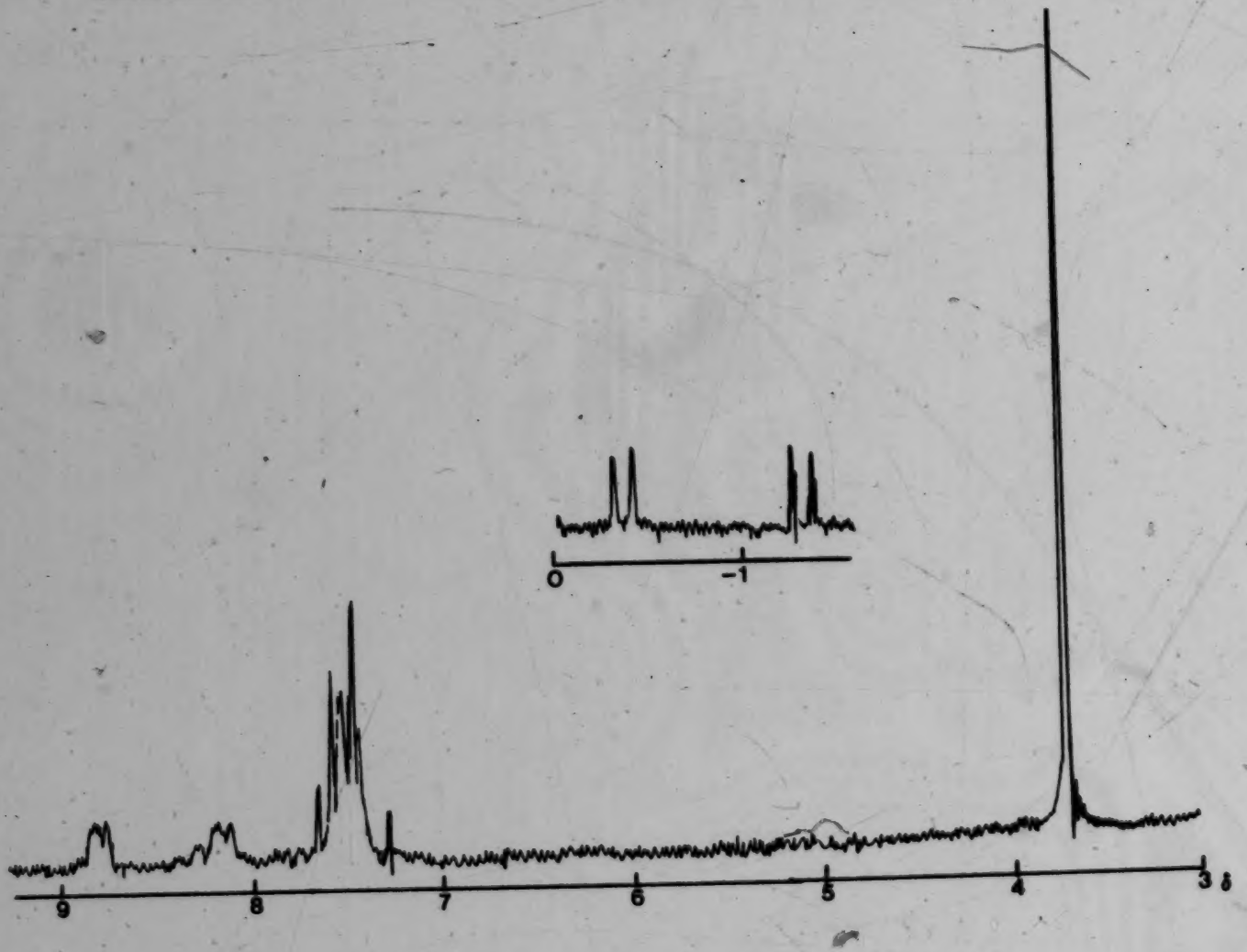
time an orange oil and a white solid corresponding to the desired product 98 and *p*-nitrobenzoic acid were collected on the cold finger. The sublimate was extracted with benzene and chromatographed on silica gel (activity IV, benzene) with the orange band being collected to give 98 in 55% yield as an orange oil. This ester derivative 98 was the least air sensitive 1,5-methano[10]annulene system and could even



be purified by ptlc in the open air. It appeared that electron withdrawal from the highly strained bridgehead olefin or from the entire delocalized system reduced the reactivity of this system toward oxygen.

The ^{1}H NMR spectrum (acetone-d_6, δ from TMS) of 98, shown in Figure 14, had the following features: 1) a doublet of doublets at -1.27, J = 10.0 Hz, J = 1.5 Hz, and a doublet at -0.34, J = 10.0 Hz, due to the methylene bridge protons, 2) a singlet at 3.80 due to the methyl ester group, and 3) the olefinic protons appeared as a multiplet of five protons centered at 7.50 and two multiplets at 8.14 and 8.78, each of one proton. The ^{13}C NMR spectrum was consistent for the structural assignment and is schematically shown in Figure 26.

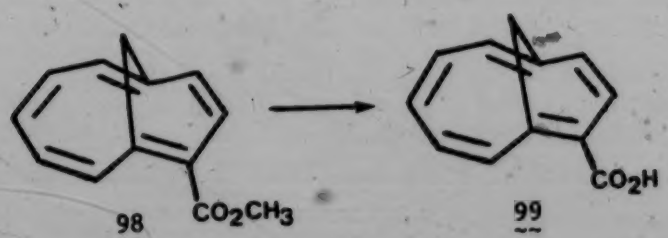
Figure 14. 100 MHz ^{1}H NMR Spectrum of 8-Methoxycarbonylbicyclo[5.3.1]undeca-1,3,5,7,9-pentaene 98



The uv spectrum showed λ_{max}^{nm} (log ε) at: 251 shoulder (4.1), 266 (4.2), 295 (4.4), 364 (3.9), and 480 (2.8). The ester carbonyl appeared at 1695 cm^{-1} in the ir spectrum. The mass spectrum was consistent, m/e calculated for $C_{13}H_{12}O_2$ = 200.0837, observed 200.0838.

The preparation of a crystalline derivative of 1,5-methano[10]-annulene was desired in order that an X-ray crystallographic study could be undertaken to provide important geometric information for this new 10π-electron system. The derivatives described thus far did not crystallize, therefore efforts to prepare a solid derivative were undertaken.

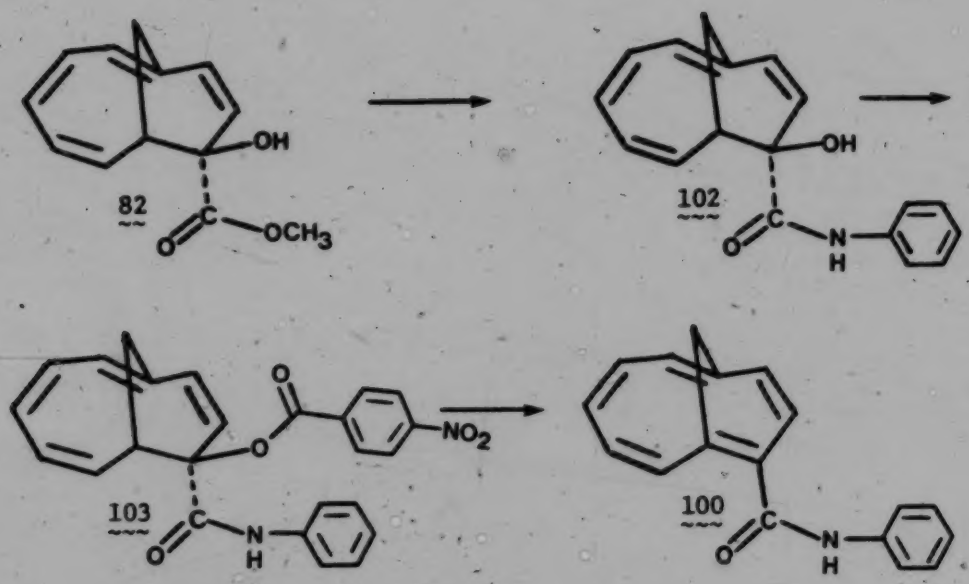
Alkaline hydrolysis of the ester 98 gave the corresponding carboxylic acid 99 as an amorphous orange solid in 25% yield. Purification of 99 was difficult and attempts to crystallize it in hexane or methanol were unsuccessful due to the sensitive nature of this compound. The acid 99, unlike the ester 98, gradually decomposed upon standing at room temperature possibly due to its acidic nature. The ^1H NMR spectrum of 99 was essentially the same as the ester 98 (see experimental).



98 99

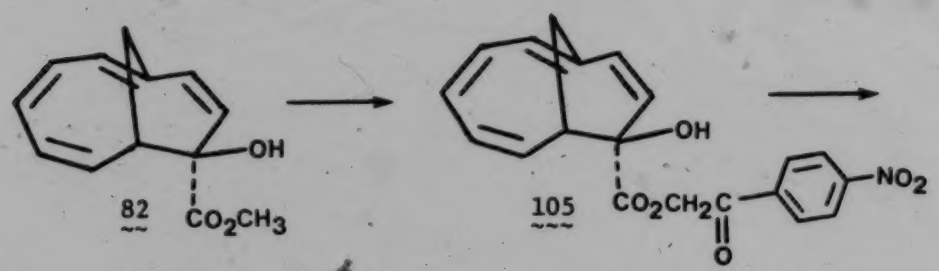
Anilides are often crystalline solids and therefore might be suitable derivatives for an X-ray analysis. Treatment of the hydroxy-ester 82 with excess lithium anilide 101 gave the hydroxyanilide 102

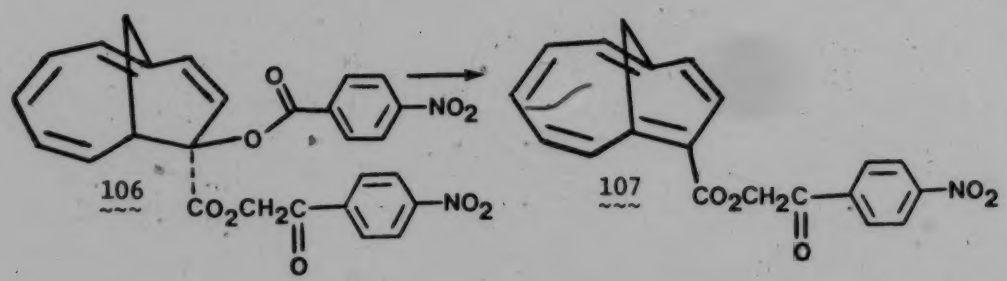
after aqueous workup and conversion of 102 to the corresponding *p*-nitrobenzoate 103 followed by pyrolysis as previously described at 300°C and 20 mm pressure gave crude anilide 100. Purification by chromatography on silica gel (activity V, 10% ethyl acetate in hexane) gave an amorphous pale orange solid. Various attempts to obtain single crystals failed.



Another attempt to obtain a crystalline derivative was directed toward the *p*-nitrophenacyl derivative of the acid 99. Alkaline hydrolysis of the hydroxy ester 82 gave the corresponding hydroxy acid 104 which was converted to the *p*-nitrophenacyl ester 105,[98] followed by conversion to the *p*-nitrobenzoate 106, and pyrolysis as before at 300°C, 10 mm, to give crude 107. Purification by chromatography on silica gel (activity V, 10% ethyl acetate in hexane) gave 107 as an orange solid which still contained impurities as determined by ^{1}H NMR analysis.

However, yellow-orange crystals were formed from hexane as fine needles which were not large enough for a crystallographic study. Attempts to collect and purify these crystals further were unsuccessful due to the gradual decomposition of 107.



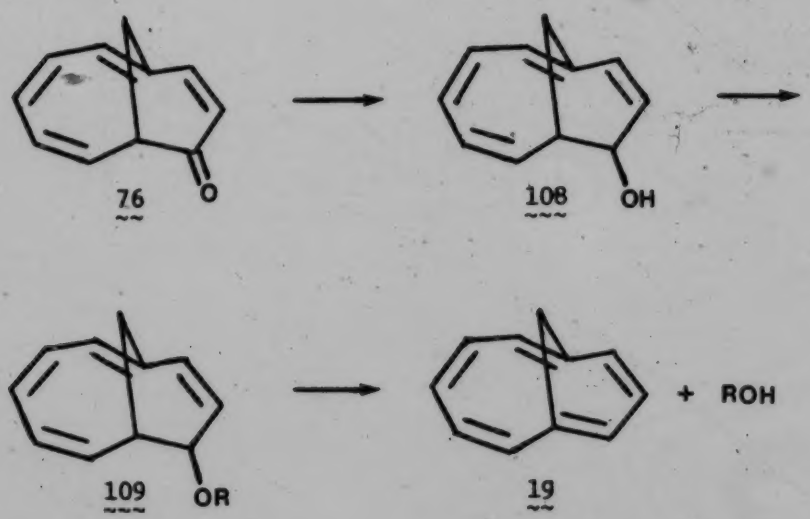


The pursuit of a crystalline derivative of 1,5-methano[10]-annulene was abandoned at this stage and efforts were directed toward the synthesis of the parent hydrocarbon.

CHAPTER 5

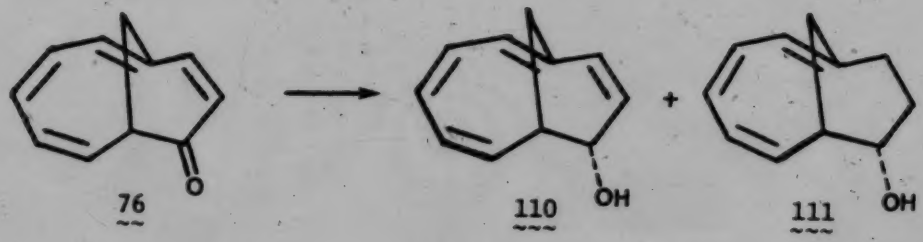
THE SYNTHESIS OF 1,5-METHANO[10]ANNULENE

The synthesis of the parent hydrocarbon 1,5-methano[10]annulene 19 seemed to be close at hand in view of the reasonably stable nature of the derivatives previously mentioned. A possible synthetic route involved reduction of the ketone 76 to the corresponding alcohol 108 which could be converted to an appropriate precursor 109 for 1,2-elimination of R-OH to 19.



Reduction of the ketone 76 with diisobutylaluminum hydride at -70°C proceeded stereospecifically to give the *endo*-alcohol 110 in 75% yield and a small amount of alcohol 111 in 8% yield. The stereochemistry of 110 was assigned on the basis of the slightly bent conformation of the ketone 76 (as shown by molecular models) which favored *exo* approach of the bulky hydride reagent. The ^{1}H NMR spectrum

($CDCl_3$, δ from TMS) of 110 showed the following features: 1) a broad doublet at 2.05, J = 12.0 Hz, which was assigned to H11a, 2) a singlet at 2.38 due to the hydroxyl proton, 3) a doublet of doublets of doublets at 3.10, J = 12.0 Hz, J = 4.0 Hz, J = 1.8 Hz, was assigned to H11b, 4) a multiplet at 3.40 was assigned to H7, 5) a multiplet at 4.65 due to H8, 6) a doublet of doublets at 5.26, J = 10.0 Hz, J = 2.0 Hz, was assigned to H9, 7) a multiplet centered at 6.00 consisting of five protons, and 8) a broad doublet at 6.4, J = 10.0 Hz, was assigned to H10. The decoupling experiments which support these assignments are summarized in Figure 15. The ^{13}C NMR spectrum was consistent with the formation of only one isomer and is outlined in Figure 26. The ir spectrum ($CHCl_3$) showed hydroxyl absorptions at 3580 and 3410 cm^{-1}. The mass spectrum was consistent, m/e calculated for $C_{11}H_{12}O$ = 160.0888, found 160.0888 and the major fragmentation was $-H_2O$ and $-H_3O$. Reduction of ketone 76 with lithium aluminum hydride gave the identical alcohol 110 in 60% yield and alcohol 111 in 20% yield.



76 110 111

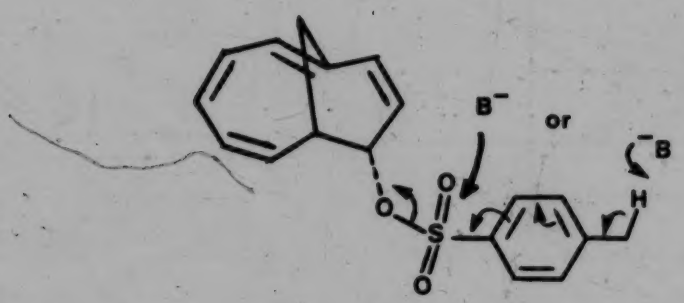
Treatment of the alcohol 110 with *p*-toluenesulphonyl chloride in pyridine gave the corresponding tosylate 112. A tetrahydrofuran solution of 112 was treated with lithium diisopropylamide (1.1 equiv) at -78°C followed by warming slowly over 1 h to room temperature and gave the alcohol 110 in 60% yield after aqueous workup. This result suggested

Figure 15. 100 MHz ^{1}H NMR DECOUPLING EXPERIMENTS FOR 110

Assignment of signals	Blank spectrum	Decoupling Frequencies (Hz) 204	309	341	467	527	611	646
		Observed decoupled signals						
H11	2.05(brd,J=12.0,1)		brs	d, J=12.0			dd J=12.0 J=4.0	
OH	2.38 (s,1)							
H11	3.10(ddd,J=12.0,J=4.0,J=1.8,1)	*		dd J=12.0 J=1.8				dd J=12.0 J=4.0
H7	3.40(m,1)	*			brs			
H8	4.65(brdt,J=7.5,J=2.0,1)			brs		brd J=7.5	dt J=7.5 J=2.0	
H9	5.26(dd,J=10.0,J=2.0,1)				d,J=10.0			s
H2,3,4,5,6	5.8-6.2(m,5)							
H10	6.44(brd,J=10.0,1)		dd J=10.0 J=2.0			s		

*The appearance of the signal is altered compared to the blank

that proton abstraction from the bridgehead position was very difficult and instead it occurred from the benzylic position of the tosylate group with subsequent fragmentation to the alcohol 110 as shown.



112

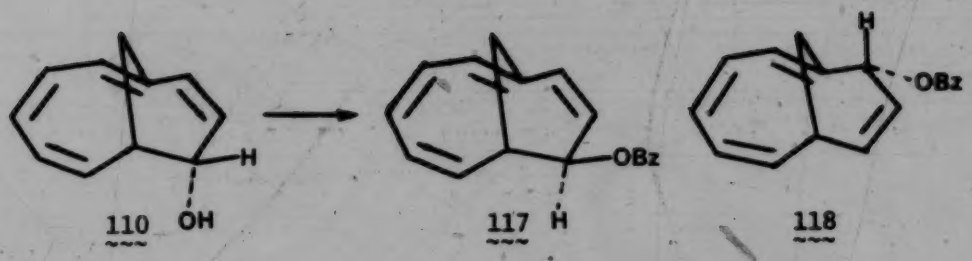
Preparation of the corresponding benzenesulphonate 113 in an analogous fashion and similar treatment with lithium diisopropylamide gave again the alcohol 110 as the only identifiable product in 50% yield. Attempted elimination of 113 with 1,5-diazabicyclo[4.3.0]non-5-ene (DBN)[100] in benzene at 40°C led only to decomposition.

Treatment of the alcohol 110 with thionyl chloride in pyridine gave an unstable chlorinated compound 114 which could not be purified. Direct treatment of the crude ether extract with lithium diisopropylamide at -78°C in tetrahydrofuran gave a red solution which remained colored after an aqueous workup. The ^{1}H NMR spectrum (benzene-d_6, δ from TMS) of the crude product showed a very interesting high field AB system consisting of a doublet of triplets at -0.96, J = 10.0 Hz, J = 2.0 Hz, and a doublet at -0.45, J = 10.0 Hz, which was good evidence for the first formation of 1,5-methano[10]annulene 19.

The doublet of triplets pattern could be predicted from the symmetry of 19 and the previously observed long range coupling between H11b and H10 in the enol ether derivatives 88 and 90, and in the ester derivative 98. Further confirmation for the formation of 19 was obtained by coupled gc-mass spectroscopy which identified a volatile peak with a mass of 142. The yield of this reaction was less than 1% (estimated by ^{1}H NMR) and attempts to improve this result failed.[101] It was therefore appropriate to find a more efficient means to prepare 19.

Attention was focused on a pyrolytic method for elimination. The *p*-nitrobenzoate 115 of 110 was prepared and an attempted pyrolysis in the same fashion as for the preparation of the ester 98 did not succeed. Heating 115 at 300°C led only to sublimation of the starting material and decomposition. Examination of molecular models indicated that a *cis* orientation for the pyrolytic elimination of *p*-nitrobenzoic acid was difficult to obtain in the *endo* configuration of 115. However, the *exo* configuration had an approximate *cis* arrangement of groups. Therefore a method to epimerize the *endo* alcohol 110 to the corresponding *exo* alcohol 116 was desired to test this hypothesis.

A method for epimerization of the hydroxyl group developed by Mitsunobu and coworkers[102] and successfully applied to sterols by A.K. Bose and coworkers[103] appeared to offer a promising solution. Treatment of 110 with two equivalents each of triphenylphosphine, benzoic acid and diethyl azodicarboxylate at -10°C for 16 h gave a mixture of two isomeric benzoates 117 and 118 in a 7:3 ratio respectively in 80% yield. The two benzoates were separated by column chromatography on silica gel and the ^{1}H NMR spectra were distinctly different. The

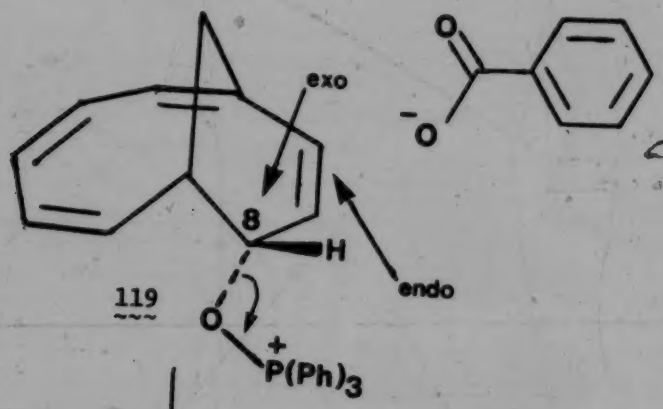


110 117 118

major product, assigned as 117 showed the following ^{1}H NMR ($CDCl_3$, δ from TMS) features from which assignments could be made on the basis of decoupling experiments: 1) a broad doublet of doublets at 2.26, J = 12.0 Hz, J = 4.0 Hz, assigned to the methylene bridge proton H11a, 2) a multiplet centered at 3.16 consisting of a doublet of doublet of doublets, J = 12.0 Hz, J = 4.0 Hz, J = 1.5 Hz, due to the other methylene bridge proton 11b, and the bridgehead proton H7, 3) a multiplet centered at 5.51 consisting of two protons due to H8 and H9, 4) a complex multiplet centered at 5.96 consisting of the five protons H2-6, 5) a broad doublet at 6.70, J = 9.0 Hz was assigned to H10, and 6) two multiplets at 7.47 and 8.08 were due to the benzoate group. The minor product assigned as 118 showed the following ^{1}H NMR ($CDCl_3$, δ from TMS) features: 1) a doublet of doublets at 2.41, J = 12.0 Hz, J = 5.0 Hz, and a broad doublet at 2.99, J = 12.0 Hz, due to the methylene bridge protons, 2) a broad multiplet at 3.45 was assigned to the bridgehead proton H7, 3) a complex multiplet centered at 6.0 consisting of eight protons, and 4) multiplets at 7.45 and 8.25 due to the benzoate group.

It was fortunate that the desired product 117 was the major reaction product. A rationale for the predominance of 117 might be

that nucleophilic attack of the benzoate anion on the intermediate 119 prefers an *exo* attack at C8 rather than an *endo* attack at C10 (which is required for the allylic rearrangement) due to the bent conformation of the bridged tetraene system.

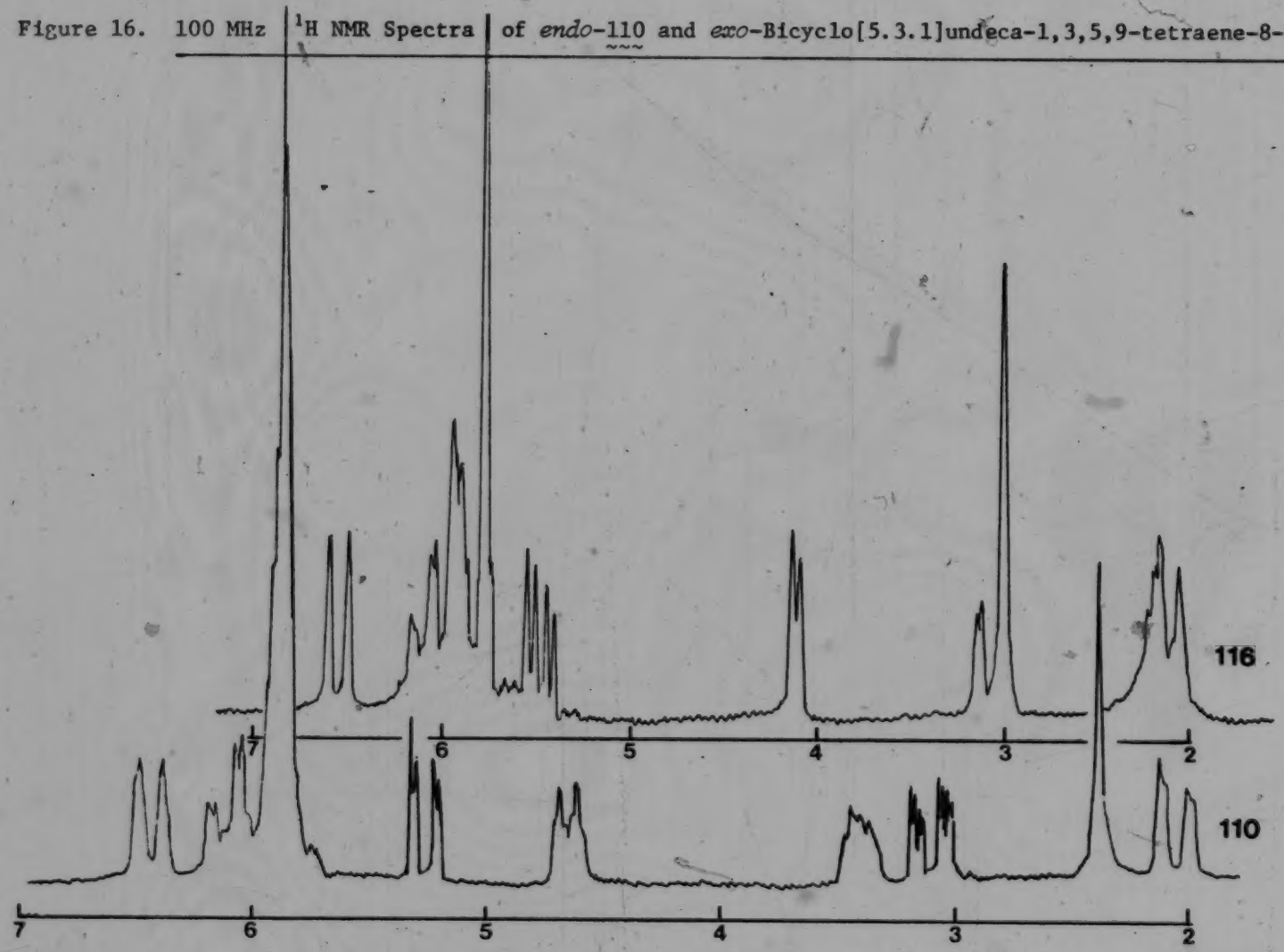


119

117 and 118

Alkaline hydrolysis of the benzoate 117 gave the *exo* alcohol 116 in 100% yield. The ^{1}H NMR spectrum ($CDCl_3$, δ from TMS) of 116 was distinctly different from that of the corresponding epimer 110 as shown in Figure 16 and showed the following features: 1) a multiplet centered at 2.12 consisting of the hydroxyl proton and a broad doublet due to

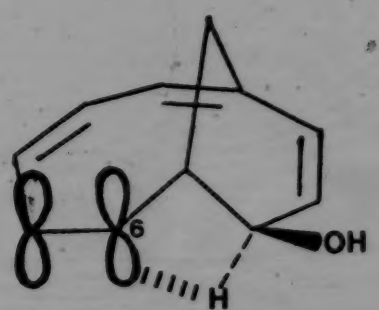
Figure 16. 100 MHz ^{1}H NMR Spectra of *endo*-110 and *exo*-Bicyclo[5.3.1]undeca-1,3,5,9-tetraene-8-ol 116.



one of the methylene bridge protons, 2) a multiplet centered at 3.10 due to the bridgehead proton H7 and the other methylene bridge proton, 3) a doublet at 4.11, J = 4.5 Hz, was assigned to H8, 4) a doublet of doublets at 5.48, J = 10.0 Hz, J = 4.5 Hz, was assigned to H9, 5) a multiplet centered at 5.95 consisting of the five protons H2-6, and 6) a doublet at 6.55, J = 10.0 Hz, was assigned to H10. The differences observed in the ^{1}H NMR spectra between the epimeric alcohols 116 and 110 are consistent with their structural assignment. The coupling $J_{7,8}$ and $J_{8,9}$ observed for each isomer in comparison to the dihedral angle obtained from molecular models is summarized below.

	Coupling		Estimated Dihedral Angles	
	$J_{7,8}$	$J_{8,9}$	H7,H8	H8,H9
110	2.0 Hz	7.5 Hz	20°	45°
116	∿ 0 Hz	4.5 Hz	90°	60°

Another interesting difference is the significant upfield shift of the H8 proton from δ4.65 in *endo* alcohol 110 to δ4.11 in *exo* alcohol 116.

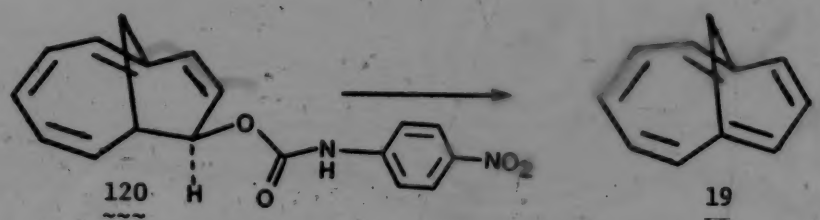


116

This shielding of H8 may be due to its close proximity to the π orbital of C6 as a result of the bent conformation of 116. The ^{13}C NMR spectrum was consistent with the structural assignment and is schematically shown in Figure 26. The mass spectrum was consistent, m/e calculated for $C_{11}H_{12}O$ = 160.0888, observed 160.0893.

With the *exo* alcohol 116 available, the choice of a suitable derivative for the intended *cis*-1,2-elimination was investigated. The same method of pyrolysis as for the preparation of 8-methoxycarbonyl-1,5-methano[10]annulene 98 was advantageous due to the experimental convenience and the small scale on which it could be performed. The features desired for the precursor for pyrolytic elimination were: 1) easy preparation from the alcohol 116, 2) facile elimination at <300°C and 3) non-volatility at this temperature at reduced pressure.

The *p*-nitrophenylcarbamate 120 appeared to meet these requirements. Treatment of a toluene solution of the *exo* alcohol 116 with *p*-nitrophenylisocyanate in the presence of triethylamine for 16 h at room temperature gave a 90% yield of 120. The ^1H NMR spectrum was consistent with the assigned structure (see experimental).



120 19

The carbamate 120 was subjected to the solid phase pyrolysis conditions by immersing the apparatus (see Figure 13) evacuated at 150 mm into an oil bath at 300°C. Immediately an orange colored sublimate appeared on the cold finger (-78°C) followed by a white sublimate. After about two minutes the flask was removed from the oil bath and the cold finger was extracted under an argon atmosphere with degassed cyclohexane. The extract was concentrated by evaporation (room temperature, 10 mm), chromatographed on silica gel under argon, and the visible orange band was collected. Evaporation of the solvent (room temperature, 10 mm) gave a 20% yield of 19 as an orange oil which solidified when cooled to -40°C and melted near room temperature. Upon exposure to air, 19 lost its color and formed a white amorphous polymer which was not soluble in cyclohexane, benzene, or acetone. The parent hydrocarbon 19 was thermally labile and had a half life of approximately 12 h when neat at room temperature (20°C). An attempt to sublime 19 at 40°C, 0.01 mm, led to decomposition. In degassed solvents such as pentane, cyclohexane, benzene, or acetone, 19 was reasonably easy to manipulate and could be stored at -80°C in pentane solution for several months. Attempts to crystallize 19 from pentane or methanol were unsuccessful mainly due to the small supply of compound, its high solubility, and its sensitive nature. The successful synthesis of 1,5-methano[10]annulene 19 provided a new model for the 10π-electron system. An analysis of its spectral properties and a comparison with those of other known 10π-electron systems was a major objective of this work and is discussed in Chapter 6.

CHAPTER 6

THE PHYSICAL PROPERTIES OF 1,5-METHANO[10]ANNULENE

The physical properties of 1,5-methano[10]annulene 19 are highly instrumental in assessing the degree of aromaticity it exhibits and further comparison of its properties to those of other 10π-electron systems is useful in predicting what properties a presently hypothetical, planar, monocyclic 10π-electron system would have.

A. ^{1}H NMR SPECTRAL ANALYSIS

^{1}H NMR spectroscopy has been described as a powerful tool for the determination of the extent of π-electron delocalization. The 100 MHz ^{1}H NMR spectrum of 19 in acetone-d_6 with cyclohexane as an internal standard and lock (taken as δ1.40) showed the following features: 1) a doublet of triplets at -0.95, J = 10.0 Hz, J = 2.0 Hz, and a doublet at -0.50, J = 10.0 Hz, which were assigned to the methylene bridge protons H11b and H11a respectively, 2) a triplet at 6.95, J = 7.5 Hz, was assigned to H9, 3) a multiplet centered at 7.45 consisting of three protons was attributed to H3, 4, and 5, 4) a doublet at 7.60, J = 7.5 Hz, consisting of two protons was assigned to H8 and H10, and 5) a doublet at 8.20, J = 8.5 Hz, consisting of two protons was assigned to H2 and H6. In order to facilitate the spectral analysis a 270 MHz ^{1}H NMR spectrum was obtained[104] and is shown in Figure 17.

Decoupling experiments illustrated in Figure 18 allowed complete assignment of the entire spectrum. Irradiation of the doublet at 8.08 reduced the multiplet centered at 7.31 to an AB_2 system consisting of the protons H3, 4, and 5. The chemical shift and the coupling values calculated[105] from the observed decoupled spectrum were used to generate

Figure 17. 270 MHz ^{1}H NMR Spectrum of 1,5-Methano[10]annulene.

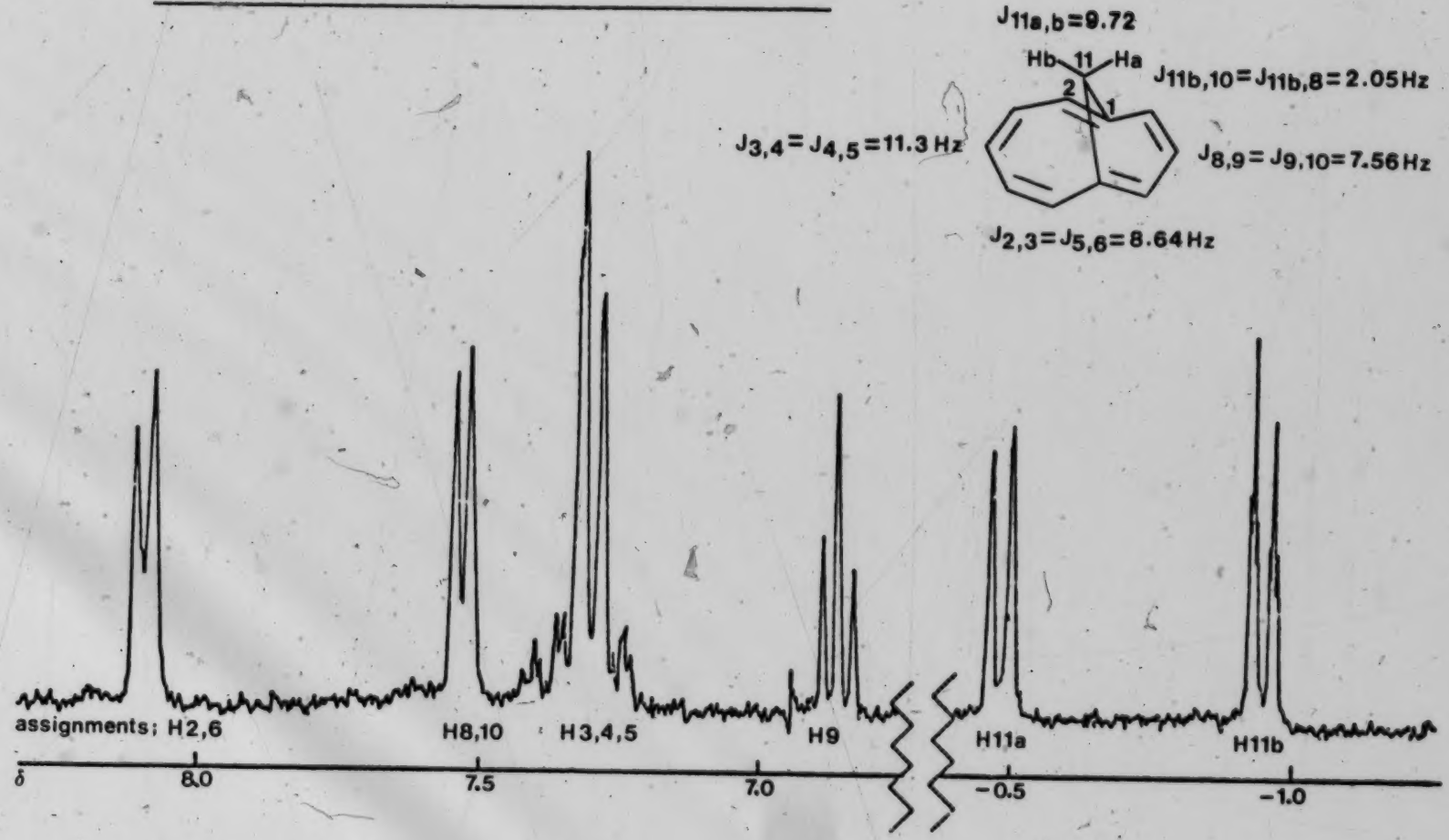


Figure 18. 270 MHz ^{1}H NMR Decoupling Experiments for 1,5-Methano[10]annulene.

Assignment of signals	Blank spectrum	Decoupling frequencies (δ)					
		-0.95	-0.48	6.86	7.30	7.52	8.08
		Observed decoupled signals					
H11b	-0.95(dt,J=9.72,J=2.05,1)		s			d,J=9.72	
H11a	-0.48(d,J=9.72,1)	s					
H9	6.86(t,J=7.56,1)					s	
H3,4,5	7.30(m,3)						AB_2 system
H8,10	7.52(d,J=7.56,2)	*		s			
H2,6	8.08(d,J=8.64,2)				s		

*The appearance of the signal is altered compared to the blank.

a spectrum using the "Iteration of Calculated NMR Spectra Using Least Square Criteria (ITRCAL)" program of Nicolet Inst. Corp. interfaced to a Bruker WP-60 FT-NMR spectrometer.[106] The observed decoupled spectra and the generated spectra matched closely as shown in Figure 19 providing support for the analysis of this AB_2 pattern. A simulated spectrum of the five spin AB_2X_2 system consisting of protons H2-6 was generated using the chemical shift and coupling data obtained from the observed spectrum in addition to guesses for the values of the allylic coupling $J_{2,4} = J_{4,6}$ and $J_{3,5}$. The best match of calculated and observed spectra for this AB_2X_2 system was found to be that with all of the allylic couplings equal to zero as shown in Figure 20. The symmetry of 19 is reflected in the equivalence of the protons H2 = H6, H3 = H5, and H8 = H10, and in the characteristic long range coupling of this system, $J_{11b,8} = J_{11b,10}$. The assignment of the methylene bridge protons is based on the previously observed long range coupling $J_{11b,10}$ in substituted 1,5-methano[10]annulene derivatives and also on the assumption that the methylene bridge is tilted toward the larger ring and thus H11b is directed into, and H11a is directed out of the shielding region of the induced diamagnetic ring current and hence H11b appears at a relatively higher field position than H11a.

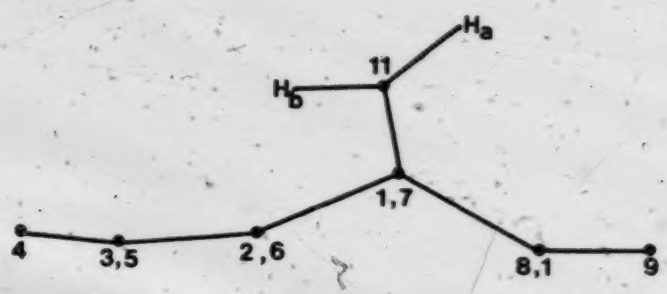
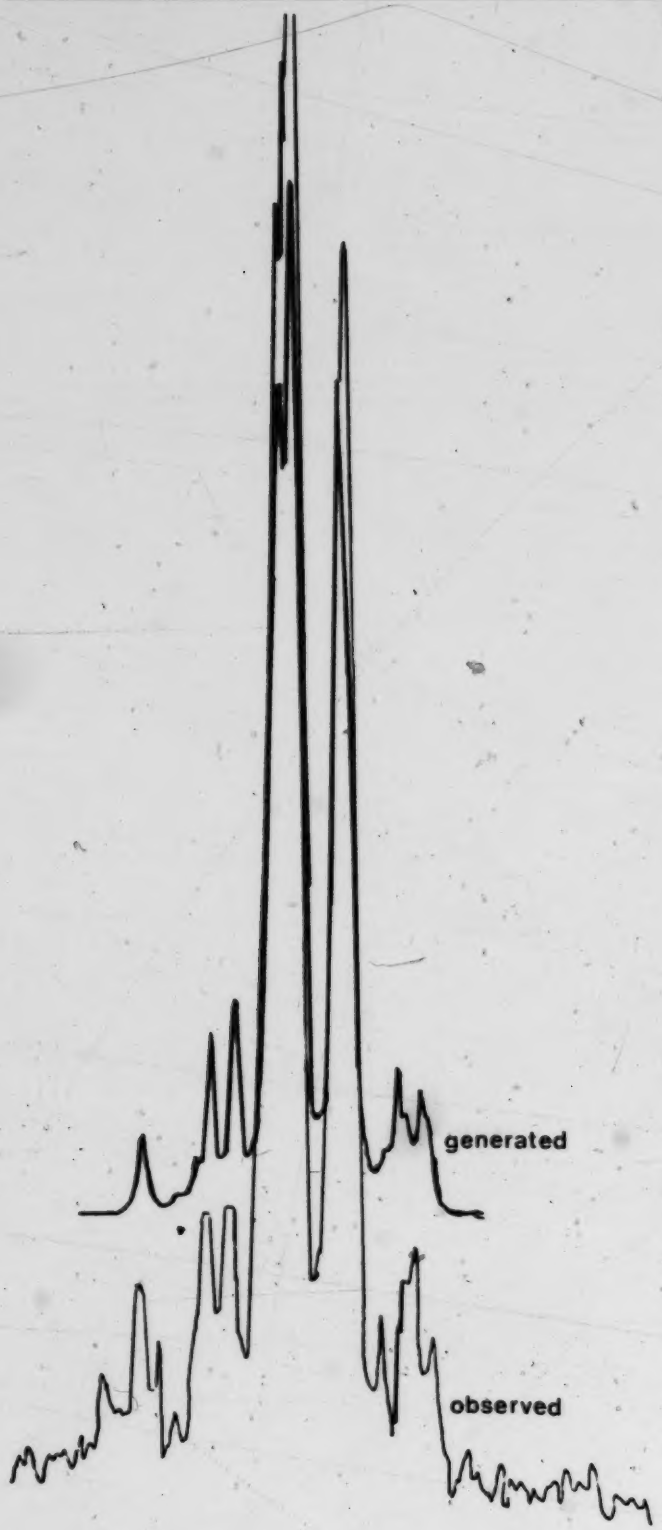


Figure 19. Generated (ITRCAL) Spectra of the Decoupled AB_2 System in 19.

Figure 20. Generated (ITRCAL) Spectra of the AB_2X_2 System in 19.



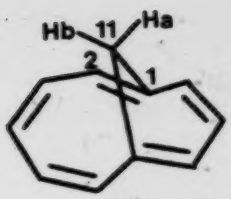
The characteristic high field signals of the methylene bridge protons of 19 clearly demonstrate an induced diamagnetic ring current. A reasonable estimate for this shielding effect on the methylene bridge protons and the corresponding deshielding of the peripheral olefinic protons 3, 4, and 5 of 19 can be obtained by comparing the chemical shifts of the same protons in the tetraene 68 as outlined in Figure 21. Similarly, the degree of induced diamagnetic ring current in 1,6-methano[10]annulene 15 can be estimated by comparison with the triene 121 (Figure 21). From this analysis, both 1,5- and 1,6-methano[10]annulene appear to be similar in their ability to sustain a diamagnetic ring current.

It should be pointed out that 1,5-methano[10]annulene 19 might possibly exist as two equilibrating bond alternate isomers D and E.

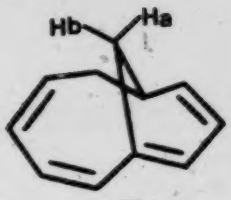
D E

Experiments were performed to investigate any temperature dependence in the ^{1}H NMR spectra of 19 and some substituted derivatives. The ^{1}H NMR spectrum of 19 in a mixture of diethyl ether-d_{10} and methylcyclohexane-d_{14} (2:1) was recorded at 0°, -50°, -80°, -110°, and -150°C and no temperature dependence was observed. The chemical shifts remained constant throughout and line broadening due to the solvent viscosity occurred from -110° to -150°C. The substituted derivatives

Figure 21. The Induced Diamagnetic Ring Current in 1,5- and 1,6-Methano[10]annulene.

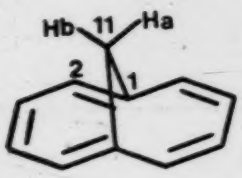


19



68

Proton	^{1}H NMR signals (δ)		Δδ
H11a	-0.50	2.50	-3.00
H11b	-0.95	2.04	-2.99
H3,4,5	7.45*	5.80*	1.65



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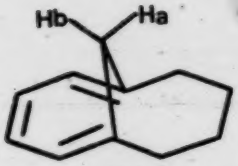


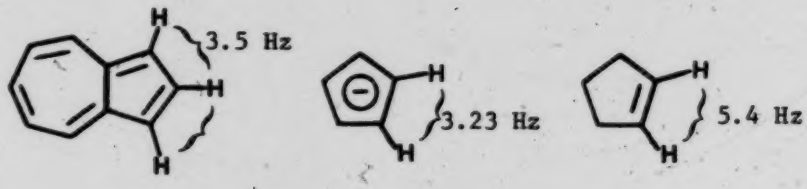
121

Proton	^{1}H NMR signals (δ)		Δδ
H11a	-0.50	2.95	-3.45
H11b	-0.50	0.80	-1.30
H2	7.20*	5.90*	1.30
H3	6.90*	6.55*	0.35

* center of multiplet

of the methoxy ester 93 and the ester 98 were investigated. Their ^{1}H NMR spectra in a mixture of tetrahydrofuran-d_8 and diethyl ether-d_{10} (1:1) were recorded at 30°, -80°, and -100°C and were identical except for some line broadening due to increased solvent viscosity below -90°C. Therefore, to the limit of the NMR time scale, 1,5-methano[10]annulene exhibits a structure of two-fold symmetry and the significant induced diamagnetic ring current in this system strongly indicates that the 1,5-methano[10]annulene system is one delocalized species.

The coupling constant of vicinal protons has been suggested as a possible indication of aromatic character.[107] A comparison of the vicinal couplings of olefinic protons of similar structures of an aromatic and a non-aromatic compound show a smaller value and a larger value for $^3J_{HCCH}$, respectively. This is clearly illustrated in azulene 17 where $J_{6,7} = J_{7,8} = 3.5$ Hz and the corresponding value found in the cyclopentadienyl anion is 3.23 Hz while the value for cyclopentene is 5.4 Hz.[107a]



The origin of this empirical observation arises from the linear relationship between the coupling constant and bond order[108] which would be expected to show an inverse linear relationship with the bond length.[109] The size of the coupling constant is sensitive to the ring size therefore only similar structures can be compared. On a very

qualitative basis a comparison of the vicinal coupling constants in similar olefin structures indirectly compares the bond length.

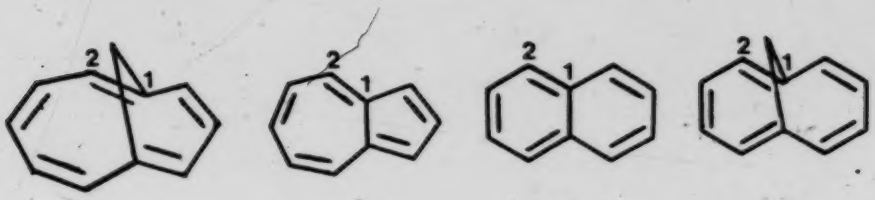
Accepting the premise that 1,5-methano[10]annulene 19 exists as one delocalized species, a comparison of the proton chemical shifts and the vicinal coupling constants of 19 with those of azulene 17,[110] 1,6-methano[10]annulene 15,[111] and naphthalene 18,[112] are shown in Figure 22.

It is noticed that $J_{8,9} = J_{9,10}$ of 19 and the corresponding couplings in azulene 17 are quite different, while the vicinal couplings in the large ring are quite similar. For 17, the vicinal coupling, $J_{8,9}$ is similar to that observed for the cyclopentadienyl anion, while for 19 this vicinal coupling has the same value as that observed for benzene. This observation indicates that the distance between C1 and C7 is likely more than 2 Å and thus the dihedral angles of $H_{8,9} = H_{9,10}$ in 19, as reflected by the vicinal coupling, may be closer to those of a six-membered aromatic system rather than a five-membered aromatic system as in azulene 17.

B. ^{13}C NMR SPECTRAL ANALYSIS

The ^{13}C NMR spectrum of 1,5-methano[10]annulene 19 was desired in order to further substantiate the symmetry of the molecule and also to possibly provide some information as to the charge density and geometry of the molecule. ^{13}C NMR chemical shifts provide a sensitive probe for local charge and changes in geometry of a given carbon atom in a molecule.[113] The relative electron density at a given carbon atom can usually be compared qualitatively in compounds of similar geometry.[114]

Figure 22. ^{1}H NMR Spectra and Vicinal Coupling Comparison.



19 17 18 15

Proton		Chemical Shifts (δ).		
2	8.08	8.22	7.67	7.27
3	7.28	6.92	7.31	6.95
4	7.34	7.20		
8	7.52	7.21		
9	7.86	7.75		
		Coupling Constants (Hz).		
$J_{2,3}$	8.64	9.5	8.29	8.97
$J_{3,4}$	11.3	10.0	6.86	9.19
$J_{8,9}$	7.56	3.5		

Some $^3J_{HCCH}$ Values for Comparison

11.8 ref. 112 | 9.6 ref. 109 | 9.64 ref. 109 | 7.56 ref. 109

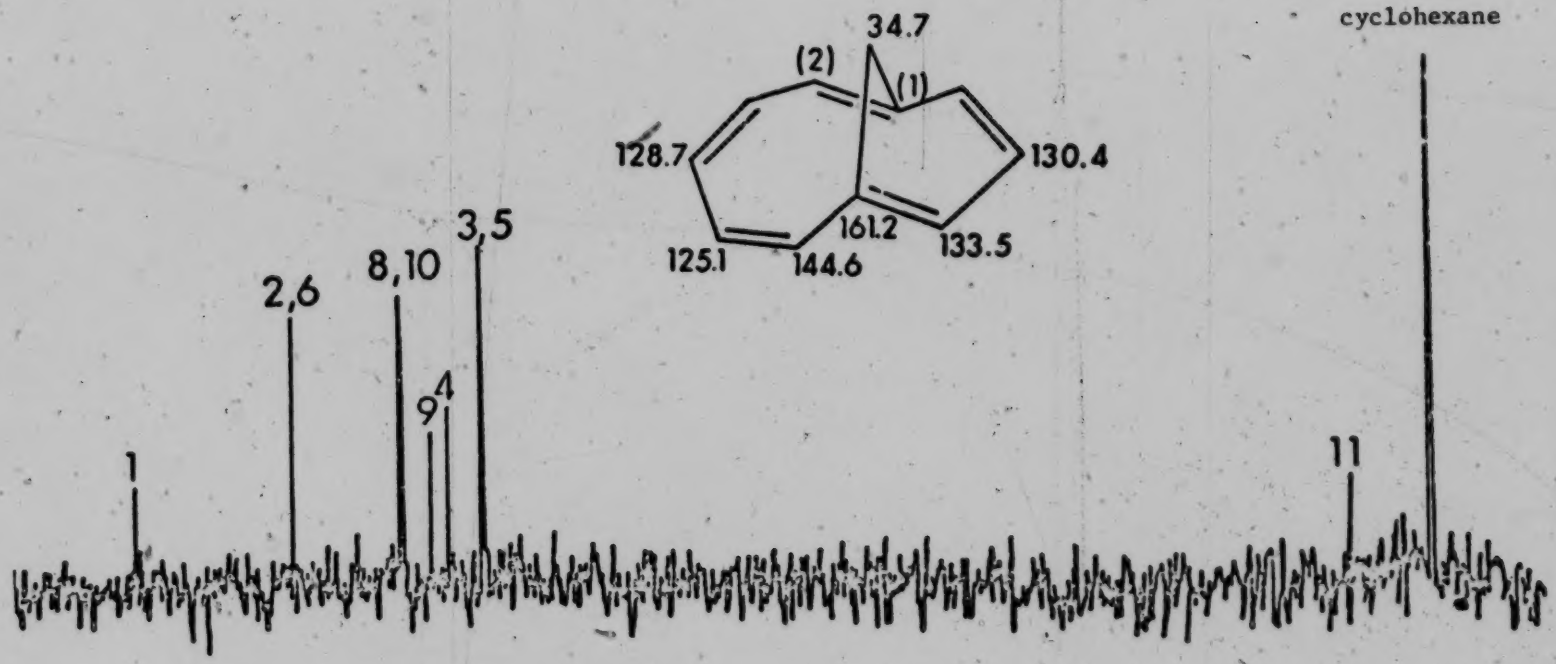
11.7 ref. 112 | 5.4 ref. 109 | 3.23 ref. 107a

^{13}C NMR has been shown to be insensitive to ring current effects.[115] The rationale for this observation is that the ring carbons of the π-system are located in a "null" region of the induced secondary magnetic field and even when a carbon atom is located ideally, as in 15 or 19, the magnitude of the shielding or deshielding is of the order of only a few ppm, which is significant for ^{1}H chemical shifts, but is outweighed in ^{13}C chemical shifts by the effects of geometry and local charge.

With the development of a microprobe assembly for obtaining ^{13}C NMR spectra on less than 20 mg of an average molecular weight compound in a reasonable time,[116] it was possible to obtain the ^{13}C NMR spectrum of 1,5-methano[10]annulene 19 with 12 mg of sample. A pentane solution of 19 at 0°C was evaporated at 10 mm pressure until it was concentrated to near neatness. Freshly distilled and degassed acetone-d_6 was added and the mixture was evaporated again and the process was repeated twice to ensure complete solvent exchange. The acetone-d_6 solution was evaporated to a volume of about 20 µl and 0.3 µl of cyclohexane was added as an internal reference.

Under an argon atmosphere, a 2.0 mm capillary sample tube was loaded using a 10 µl syringe to a total volume of 30 µl. The concentration of the sample was therefore about 2.8 M in 19. The noise decoupled spectrum was obtained with 2000 scans at 0°C and at -80°C and showed no differences except that the relative intensities of the signals changed. The ^{13}C NMR spectrum (ppm from TMS) of 19 is shown in Figure 23 and clearly demonstrates a two fold symmetry for 19 as only seven different carbon signals were observed. The signal at 34.7 was readily assigned to the bridge methylene C11. The signals at

Figure 23. 22.63 MHz ^{13}C NMR Spectrum of 1,5-Methano[10]annulene with Assignments.



125.1, 133.5, and 144.6 appeared to contain two carbons each by their relative intensity compared to other signals. The bridgehead carbons C1 and C7 were expected to show a signal of double intensity but this might appear less intense due to the relatively long relaxation time usually observed for quaternary carbons.[117] The bridgehead carbons were identified as the signal at 161.2 by the technique of modulated off-resonance decoupling.[118] The remaining carbon signals were assigned by recording the ^{13}C NMR spectrum while selectively decoupling the ^{1}H NMR spectrum.[119] A description of these experiments is summarized in Figure 24. On the basis of these results the complete assignment of the ^{13}C NMR spectrum was possible and is shown in Figure 23.

A comparison of the ^{13}C chemical shifts of 1,5-methano[10]-annulene 19, azulene 17,[120] 1,6-methano[10]annulene 15,[121] and naphthalene 18,[122] is shown in Figure 25. A distinct difference in the chemical shift of the bridgehead carbons of 19 and 15 is apparent. 1,6-Methano[10]annulene 15 exhibits an unusually high field chemical shift at 114.8 for the bridgehead carbons demonstrating unique electronic properties which may, in part, be due to some transannular interaction between C1 and C6. The other carbon signals of 15 are almost identical to the corresponding carbon signals in naphthalene 18. The bridgehead carbons of 19 appear at an unusually low chemical shift for sp^2 hybridized carbon in a hydrocarbon environment, at about 47 ppm lower than those of 15 and about 20 ppm lower than those of azulene 17. This observation suggests either a geometric difference and/or a decreased electron density at C1 and C7 in 1,5-methano[10]annulene compared to the other 10π-electron systems.

Figure 24. Selective ^{1}H Decoupling of the ^{13}C NMR Spectrum of 1,5-Methano[10]annulene.

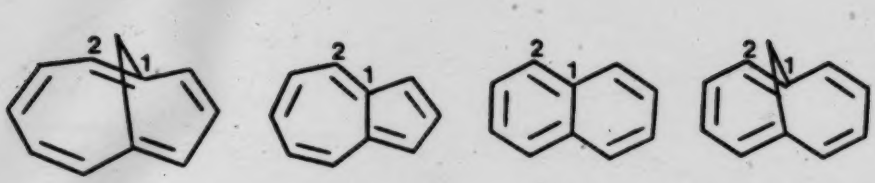
Assignment of carbon signals	Blank ^{13}C noise decoupled spectrum (off resonance decoupling multiplicity)	^{1}H NMR decouplings (δ)			
		6.88	7.38	7.55	8.15
		Observed enhanced ^{13}C signals			
C11	34.7 (t)				
C3,5	125.1 (d)	*	x	-	
C4	128.7 (d)		*	-	
C9	130.4 (d)	x			
C8,10	133.5 (d)		-	*	
C2,6	144.6 (d)				x
C1,7	161.2 (s)				

x Strong enhancement

* Medium enhancement

- Small enhancement

Figure 25. ^{13}C Chemical Shift Comparison.



19 17 18 15

Carbon	Chemical Shifts (ppm from TMS)			
1	161.2	140.8	133.9	114.8
2	144.6	136.9	128.3	128.7
3	125.1	123.2	137.4	
4	128.7	137.4		
8	133.5	119.2		
9	130.4	137.9		
11	34.7			34.8

The sensitivity of variable temperature ^{13}C NMR spectroscopy for the detection of valence tautomers and bond shifts is well recognized. One of the first applications of ^{13}C NMR to dynamic phenomena was demonstrated by Masamune and coworkers[123] for the [10]annulene 5. This method has also been used for the elucidation of valence tautomerism in 1,6-methano[10]annulenes substituted at C11.[56]

The ^{13}C NMR spectra (acetone-d_6) of the parent hydrocarbon 19, the ester 98, and the methoxyester 93 recorded at room temperature and at -80°C were temperature independent with respect to the observed chemical shifts. Only the relative intensity of the signals changed with the quaternary carbons being more intense at the lower temperature. This result, together with the ^{1}H NMR variable temperature studies supports the conclusion, although tentative at the present time, that the 1,5-methano[10]annulene system is one delocalized species.

A compilation of the ^{13}C chemical shifts of the various 1,5-methano[10]annulene compounds prepared and some of the bicyclo[5.3.1]-undecane precursors are schematically shown, along with the multiplicity observed under the conditions of off-resonance decoupling, in Figure 26.

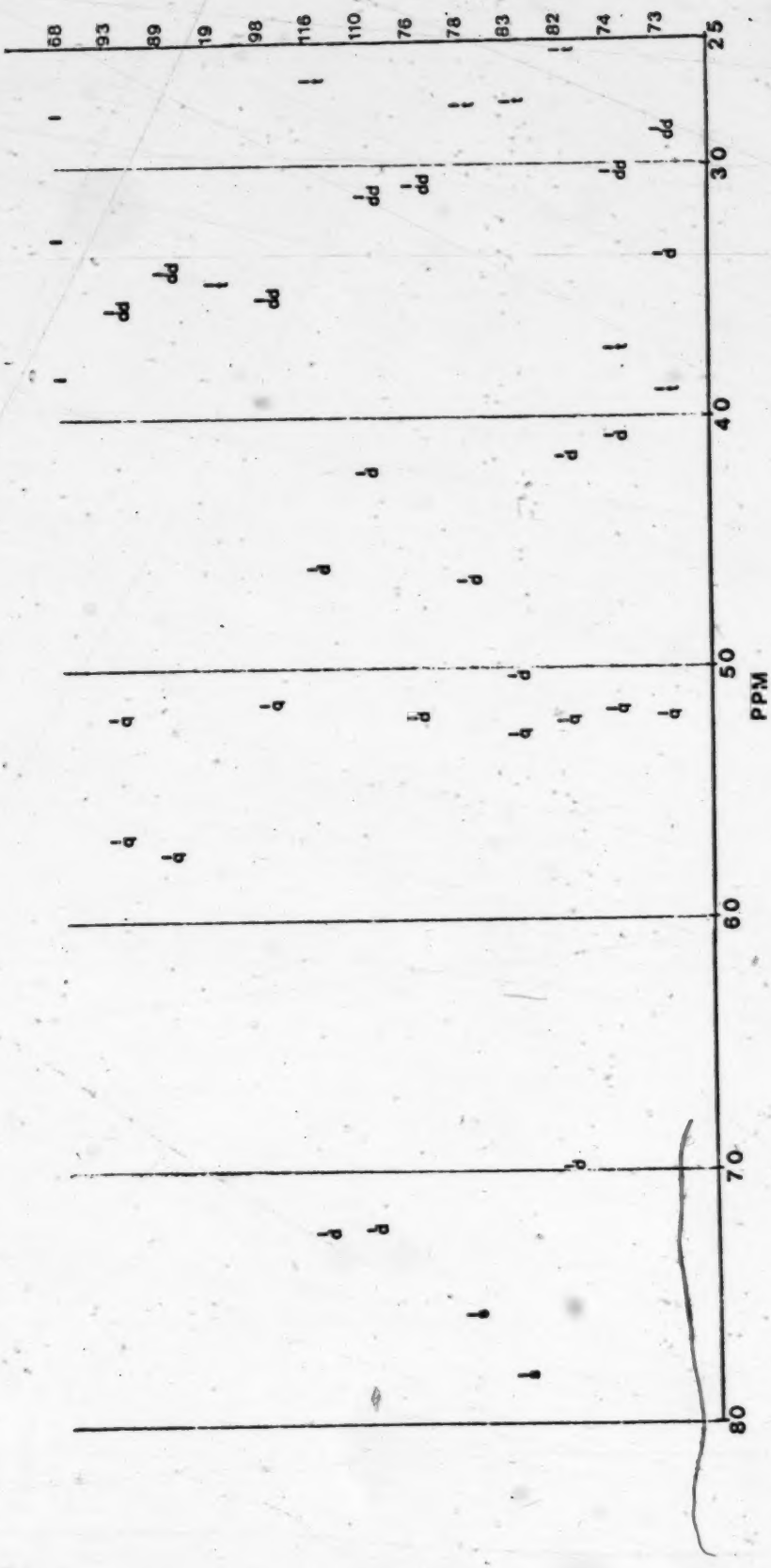


Figure 26. Compilation of ^{13}C Chemical Shifts

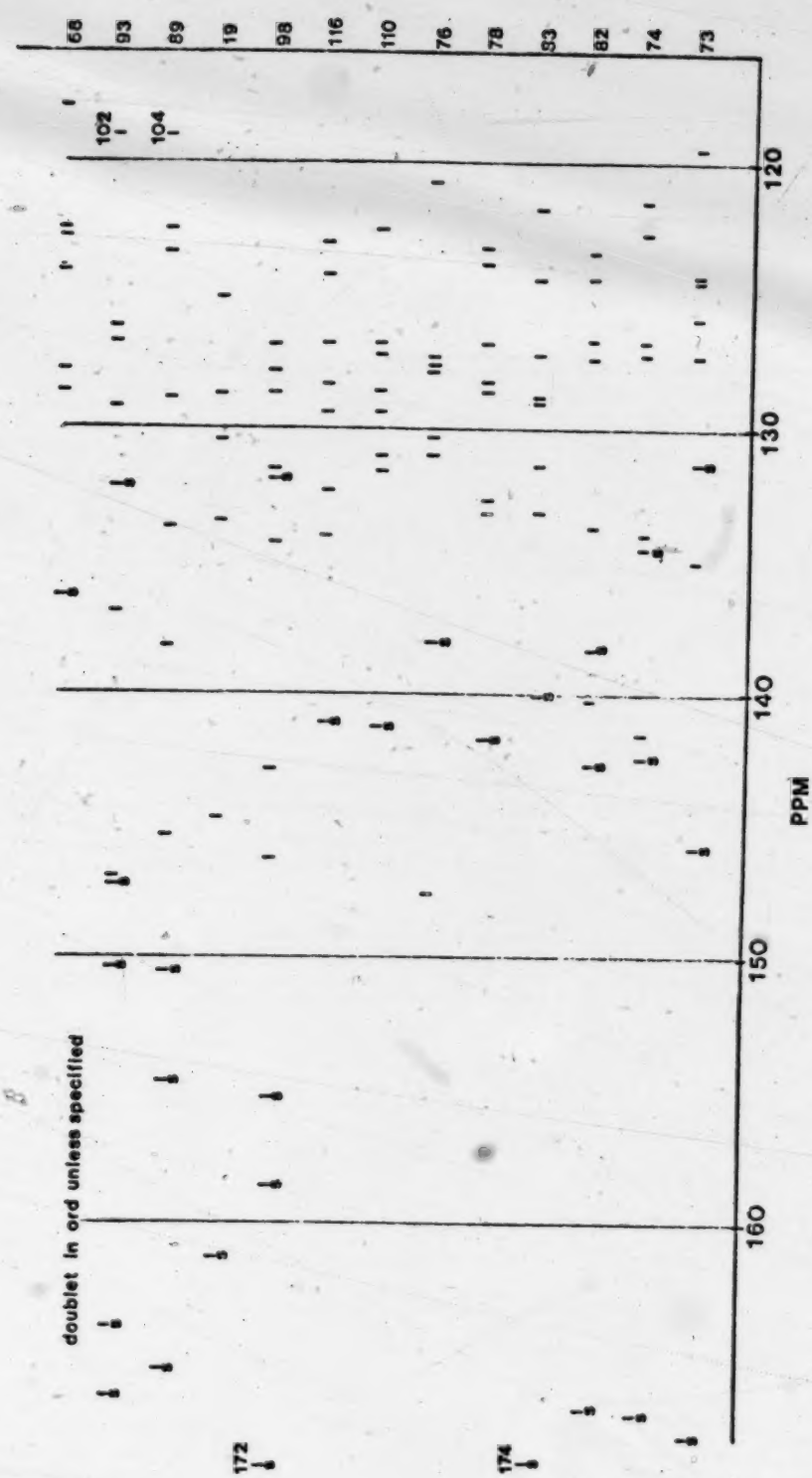


Figure 26. (Continued).

C. ULTRAVIOLET AND VISIBLE SPECTRA

The electronic absorption of 1,5-methano[10]annulene 19 extends into the visible region and shows the following λ_{max} nm (log ε) in cyclohexane: 210 (3.9), 255 (4.0), 282 (4.4), a shoulder at 297 (3.9), a shoulder at 303 (3.8), 325 (3.5), and 480 (2.5). A comparison of the electronic absorptions of 19, 17,[124] 15,[53] and 18[125] is shown in Figure 27. There is a close similarity between the overall features of the spectra of 1,5-methano[10]annulene 19 and azulene 17. The electronic absorption of several substituted 1,5-methano[10]annulene compounds are compared in Figure 28. Possible perturbation of the 10π-electron system by the various substituents is reflected in the differences in the λ_{max} and extinction coefficients (ε) observed.

The electronic absorption spectra of the 1,5-methano[10]annulene system exhibits characteristics of a highly delocalized π-electron system which agrees with the conclusion derived from the NMR spectra. The possibility that this 10π-electron system exists as a fast equilibration of bond alternate forms is probably quite remote. With the current knowledge of the electronic structure of this system, further discussion of the uv spectra appears to be at best, speculative.

Figure 27. Absorption Spectra Comparison of 10π-Electron Systems.

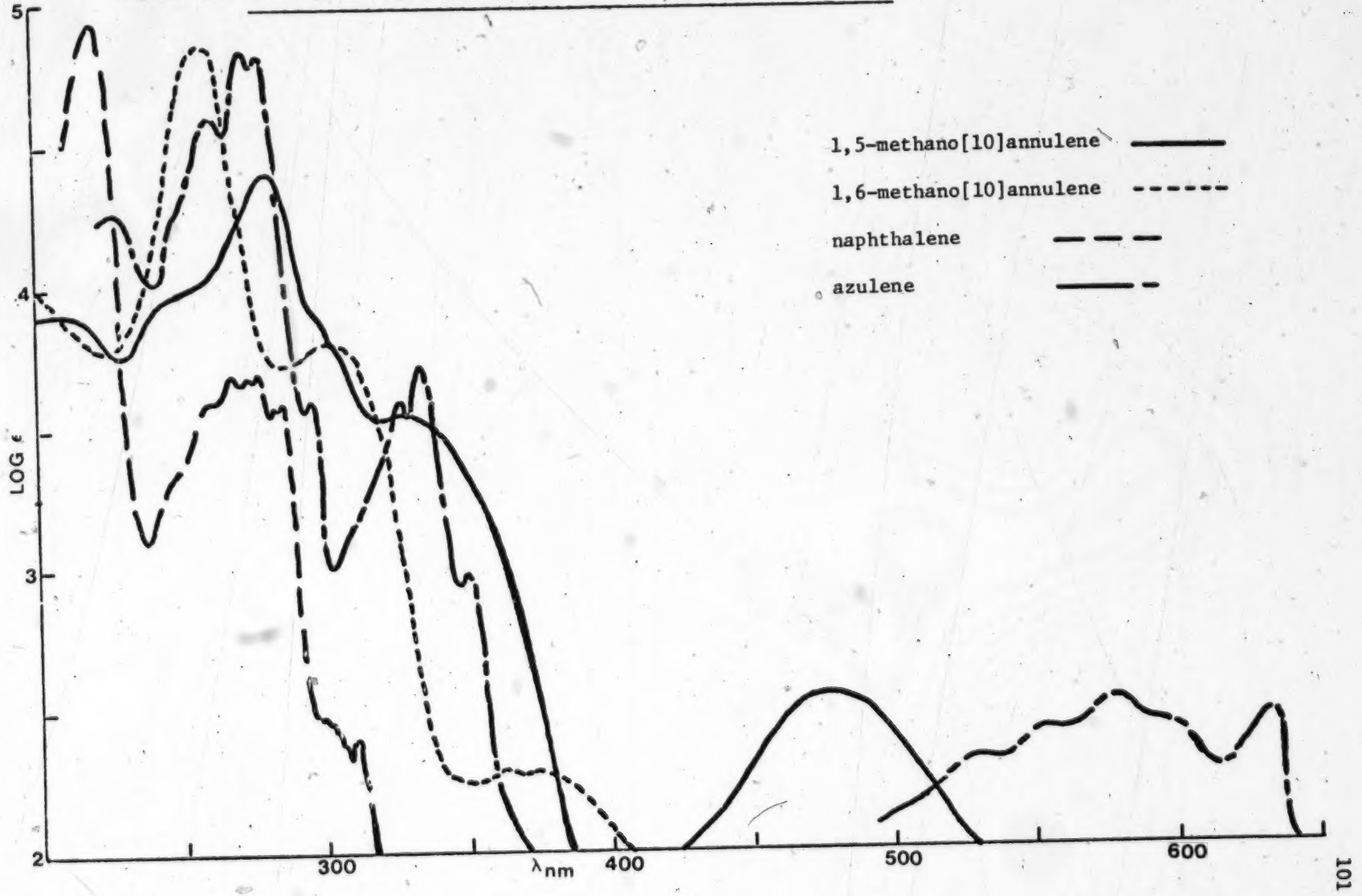


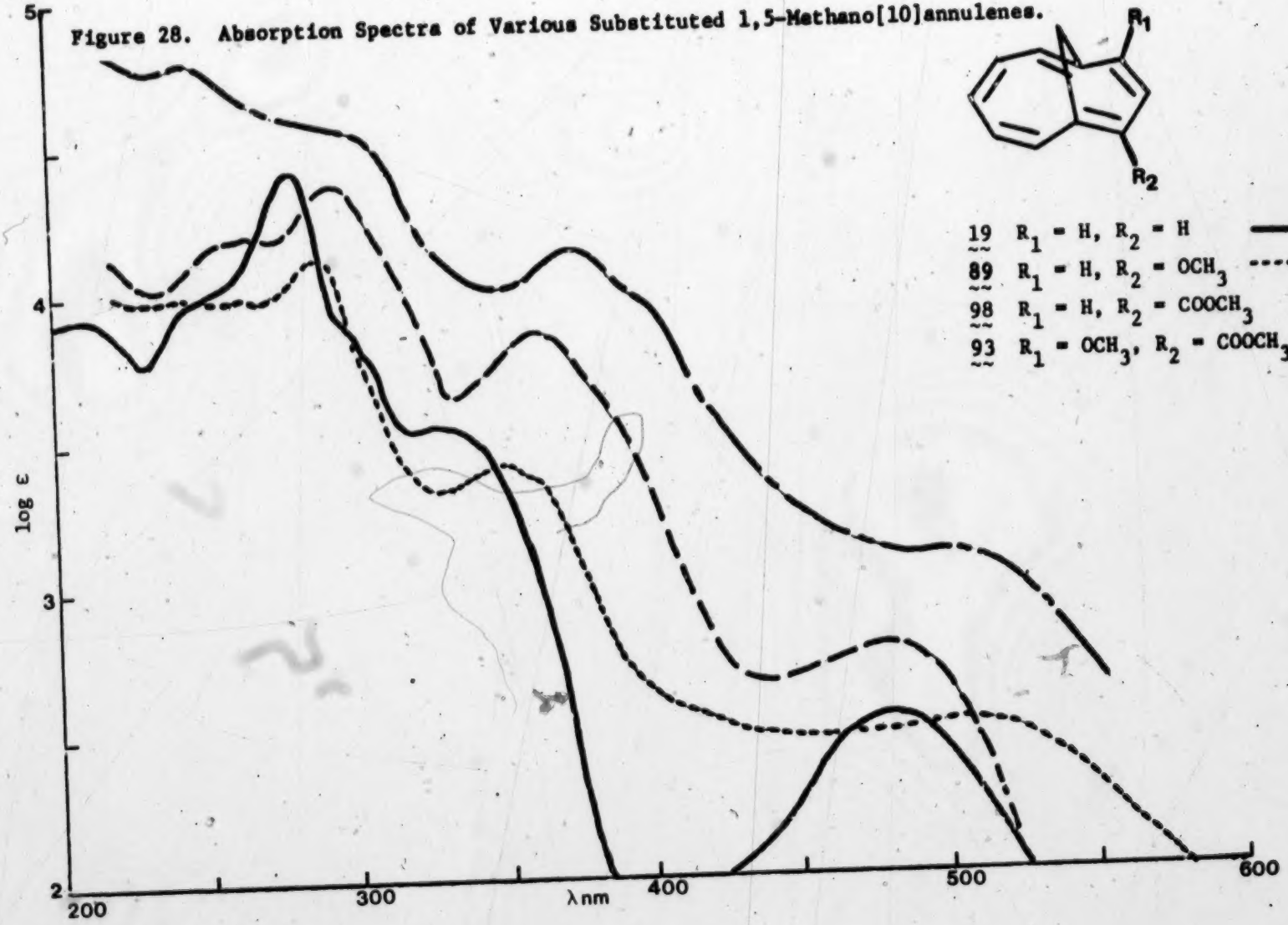
Figure 28. Absorption Spectra of Various Substituted 1,5-Methano[10]annulenes.

19 R_1 = H, R_2 = H

89 R_1 = H, R_2 = OCH_3

98 R_1 = H, R_2 = $COOCH_3$

93 R_1 = OCH_3, R_2 = $COOCH_3$

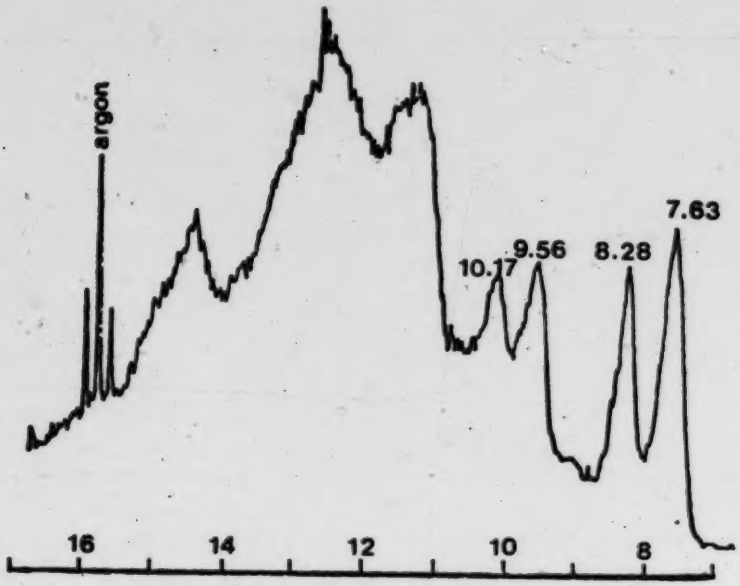


D. PHOTOELECTRON SPECTRA

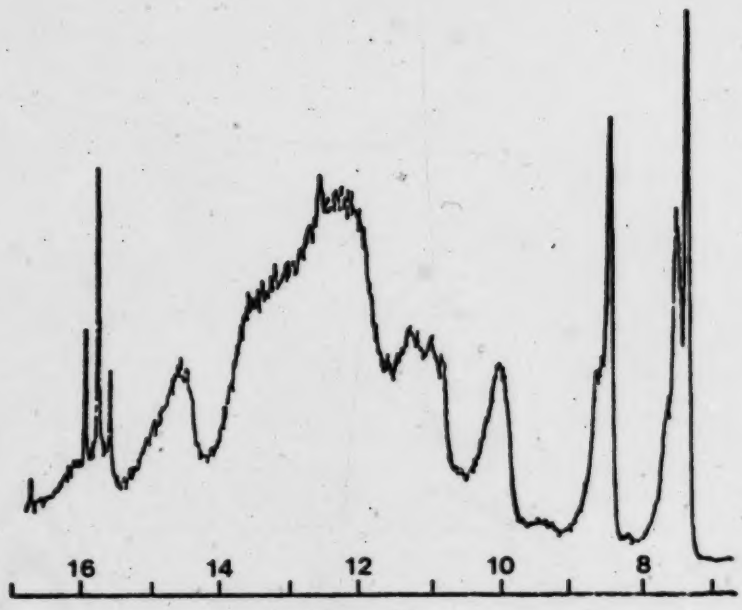
Photoelectron (PE) spectroscopy at first sight appeared to be an attractive means of determining aromatic character in that it seemed to give a value for the electron energy levels of a molecule.[126] In the photoelectron experiment, a photon of known energy, $h\nu$, is directed at a molecule, A, and the kinetic energy of the ejected electron is measured. Since only the total energy of a molecule is a well defined quantity and not the energy of the individual electrons, the electron energy levels are not really being measured in the photoelectron experiment but rather the difference between the total energy of the neutral molecule and the total energy of the positive ion is being measured. After an electron has been removed the positive ion may be in various states involving extensive rearrangement of the remaining electrons, therefore the electron energy levels determined by photoelectron spectroscopy may not have relevance to the ground state of molecules. An example[127] which demonstrates this problem is illustrated for cyclooctatetraene which has an ionization potential of 8.04 eV while ethylene has 10.5 eV. This result does not mean that there is extensive interaction between double bonds of cyclooctatetraene. Instead, it demonstrates that the positive ion formed when an electron is ejected from cyclooctatetraene undergoes electron reorganization which is reflected as removal of an electron partly from some or all of the four double bonds. The relevance of ionization potentials as a measure of aromaticity is therefore limited but does provide another spectral method of observing the electronic properties of a molecule.

The photoelectron spectra of 1,5-methano[10]annulene 19,[128] and azulene 17[129] are shown in Figure 28 and can be compared to the photo-

Figure 29. Photoelectron Spectra of 1,5-Methano[10]annulene 19 and Azulene 17.

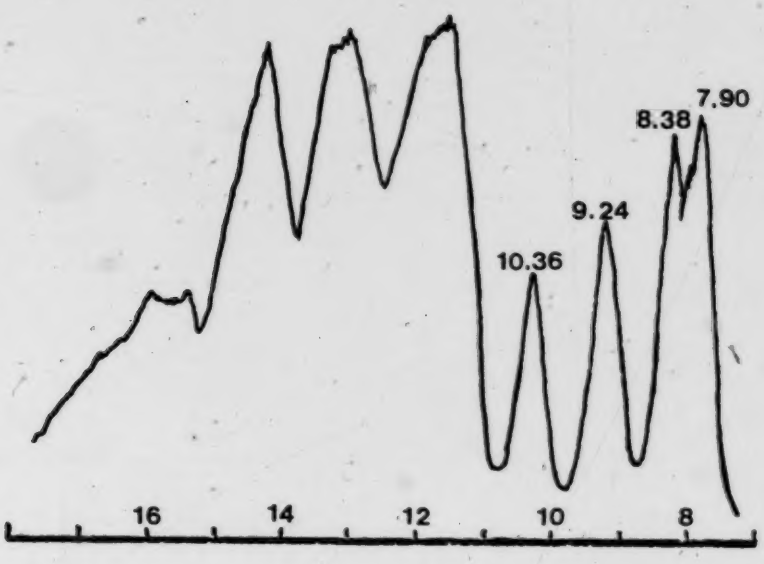


1,5-Methano[10]annulene 19

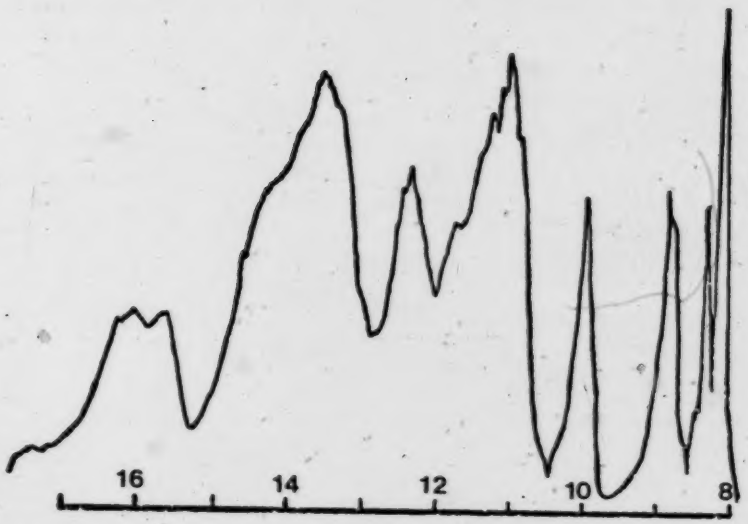


Azulene 17

Figure 30. Photoelectron Spectra of 1,6-Methano[10]annulene 15 and Naphthalene 18.



1,6-Methano[10]annulene 15

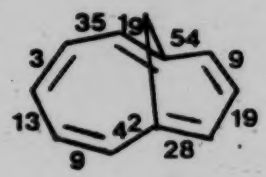


Naphthalene 18

electron spectra of 1,6-methano[10]annulene 15[54] and naphthalene 18[130] as shown in Figure 29. The gross features show that the PE spectrum of 1,5-methano[10]annulene 19 is similar to azulene 17 and that of 1,6-methano[10]annulene 15 is similar to naphthalene 18. The first ionization potential of 19 is lower than that of 15 by 0.27 eV. An analysis of the PE spectrum of 1,6-methano[10]annulene 15 has been reported by Boschi and coworkers.[54] They concluded that the PE spectrum of 15 closely parallels that of naphthalene and stated that 15 "does not show the full amount of π-electron delocalization expected for a hypothetical planar [10]annulene". The analysis of the PE spectra requires a computation of the energy levels of the molecule and a MINDO-3 calculation has been performed for 19. However, the absence of an exact experimental geometry (X-ray structural analysis) for 19 causes the reliability of such an empirical treatment to be questionable. Therefore it is not possible to confidently analyse the PE spectrum of 19 at this time.

E. CONCLUSION

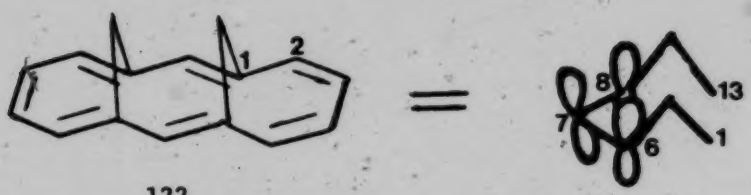
Theoretical calculations by Allinger and Sprague[131] predicted that the σ system constraints of 1,5-methano[10]annulene 19 would force ring dihedral angles to differ up to 54° and therefore 19 would have complete bond alternation. The calculated dihedral angles for 19 are shown below and the average distortion from planarity is about 23°. A similar calculation for 1,6-methano[10]annulene predicted geometric



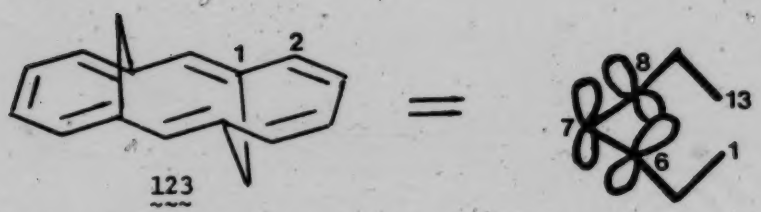
parameters which were in good agreement with the X-ray structure determination of the 2-carboxylic acid derivative of 15. The dihedral angles of the conjugated system of 15 are distorted less than 30° and have an average distortion of about 19°. This calculation therefore predicted that these isomeric 10π-electron systems 19 and 15 would be quite different.

The ^{1}H NMR spectra observed for the 1,5-methano[10]annulene system demonstrated the existence of a highly delocalized 10π-electron system as reflected by the induced diamagnetic ring current. An impressive demonstration of the effect of the molecular geometry on the ability of a cyclic π-electron system to sustain a diamagnetic ring current has been shown by Vogel and coworkers[132] for the bismethano[14]-annulene system. The ^{1}H NMR spectra of syn 122 and anti 123 were fundamentally different, with 122 exhibiting the presence of an

induced diamagnetic ring current while 123 showed signals typical of a cyclopolyolefin. The approximate geometry as shown by molecular models indicated that 122 was almost planar while 123 was severly distorted from planarity, especially at the bridging positions. An X-ray structural analysis of 123 confirmed the nonplanar geometry with dihedral angles of adjacent $2p_z$ atomic orbitals approaching values up to 70°.[133]



122



123

The degree to which the 1,5-methano[10]annulene system assumes a planar conformation may be greater than that shown by simple molecular models or by the theoretical treatment.[131] This gain in stabilization energy may in the case of 1,5-methano[10]annulene 19 be greater than the structural strain energy generated to allow effective π-bond overlap. This is in contrast to the monocyclic cyclopentaenes 4 and 5 where the geometrical constraints were greater than the energy gain by π-electron delocalization. To what extent 1,5-methano[10]annulene 19 acquires a

planar conformation is presently not known.

Aromatic molecules such as benzene have planar and rigid structures, and obviously, a dihedral angle of 0°C provides the most effective overlap of $2p_z$ atomic orbitals. However, nature might allow greater geometric flexibility for effective π-bond overlap. Both experimental and theoretical studies are probing this concept and there are indications that aromatic systems are capable of 5°-20° deviations from planarity without a significant loss of energy[134]. The bridged [10]annulenes 15 and 19 demonstrate a delocalized π-electron system even with significant (20° and possibly greater) deviations from planarity.

When the two models 19 and 15 for a hypothetical monocyclic delocalized 10π-electron system are compared to the bicyclic fused 10π-electron systems azulene 17 and naphthalene 18, it is observed that 1,5-methano[10]annulene 19 is similar to azulene 17 and 1,6-methano-[10]annulene 15 is similar to naphthalene 18. This observation indicates that transannular interactions in 19 may be minimized compared to 15. Thus, 1,5-methano[10]annulene might represent possibly the closest model yet prepared for a hypothetical, planar, monocyclic 10π-electron system in which virtually no transannular interaction exists, and therefore, allows a clearer experimental assessment of the properties of this type of electron arrangement. Unfortunately, the absence of geometric data for the 1,5-methano[10]annulene system precludes any attempt to quantitatively analyse its electronic structure. An X-ray crystallographic analysis of 19 and theoretical treatments based on this geometric data remain to be carried out in order to conclude the

study of this new 10π-electron system.

At the onset of this work, the synthesis of 1,5-methano[10]-annulene 19 was of interest for two main reasons: 1) the monocyclic [10]annulenes 4 and 5 appeared to be more labile than expected in view of the stability of 1,6-methano[10]annulene and 2) to examine the extent to which a possible transannular interaction in 15 stabilizes the monocyclic 10π-electron system. Now with 1,5-methano[10]annulene 19 available, it has been observed that although 19 does possess a significant amount of structural strain, as indicated by its oxygen and thermal sensitivity, it indeed does possess a delocalized 10π-electron system as evident by the induced diamagnetic ring current. With this new model, it can be concluded that a delocalized array of 10π-electrons does represent a stabilized aromatic system as originally predicted by Hückel.[135,136]

CHAPTER 7

EXPERIMENTAL

All experiments were conducted under an inert atmosphere of argon or nitrogen. The solvents and reagents used in each experiment were dried and purified by accepted procedures unless otherwise stated.[137] A rotary evaporator (water aspirator vacuum) was used for the removal of solvents where "evaporation under reduced pressure" is mentioned.

Melting points and boiling points are uncorrected.

The ultraviolet and visible spectral data were obtained on a Unicam SP 1800 ultraviolet spectrophotometer. The λ_{max} values are reported in units of nanometers followed in brackets by the logarithm of the molar extinction coefficient (log ε).

The ^{1}H NMR spectra were obtained using a Varian Associates A-60, HA-100, HA-100 equipped with a Digilab FT-NMR pulse and data system, or a Bruker WP-60 FT spectrometer. The ^{13}C NMR spectra were obtained using a Bruker HFX-100 spectrometer. Tetramethylsilane was used as an internal standard unless otherwise stated. The ^{1}H NMR spectral data are reported with the chemical shift in δ units followed in brackets by the signal description (multiplicity), the first order coupling constant value in Hz when appropriate, the relative integration value, and an assignment of the signal when possible. The following abbreviations are used in the signal description.

s; singlet	quin; quintet
d; doublet	sept; septet
t; triplet	m; multiplet
q; quartet	br; broad

The ^{13}C NMR spectral data are reported with the chemical shifts in δ units followed in brackets by the multiplicity observed during off-resonance decoupling and an assignment of the signal when possible.

The infrared spectra were obtained on a Perkin-Elmer Model 257 infrared spectrometer. The absorption signals are reported in cm^{-1} followed by a description of the signal using the following abbreviations.

s; strong	w; weak
m; medium	br; broad

Only the major absorptions are reported.

The mass spectra were obtained with an A.E.I. MS-50 high resolution mass spectrometer. The mass spectral data are reported as the m/e values for the molecular fragments followed in brackets by the relative abundance and the molecular formula for the respective fragment. Only the major fragments are reported.

The gas-liquid phase chromatographic analyses were performed on a Hewlett-Packard model 7620 research chromatograph equipped with 1.8 m x 0.3 cm columns and a flame ionization detector. The conditions and type of column used are described in the text for each case.

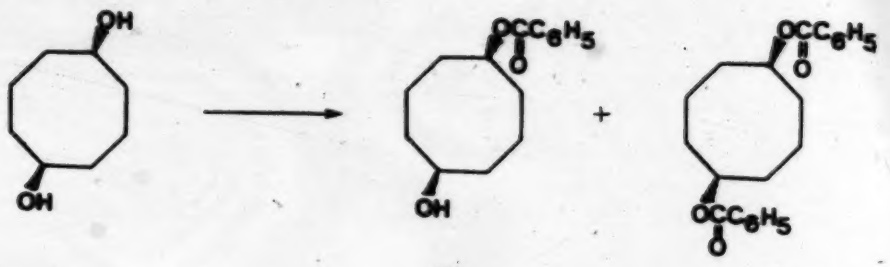
Thin layer chromatographic analysis was performed using Woelm Silica Gel F254, 0.25 mm thick, 20 x 20 cm plates cut in the appropriate sizes. Preparative thin layer chromatography was performed on 1.0 mm thick, 20 x 20 cm plates prepared from an aqueous slurry of silica gel EM^{R}, HF 254 and 366 (type 60) without binder. The plates were activated by drying at 110°C for 16 h and stored under anhydrous conditions.

Column chromatography was performed using MN^{R}, Silica Gel 60, 70-270 mesh, activity I unless oth[illegible]se stated. Different activities

of silica gel were obtained by adding silica gel to the appropriate amount of water contained in a flask and rotating or shaking the mixture for 30 min until a homogeneous adsorbent was obtained. The following recipe was used.

Activity Grade	II	III	IV	V
Water added (% by weight)	10	12	15	20

cis-5-hydroxycyclooctyl benzoate 58



58

To a stirred solution of *cis*-1,5-cyclooctanediol (20 g, 0.14 mol) in pyridine (250 ml) at room temperature was added benzoyl chloride (16.5 ml, 0.14 mol). After stirring for 1.5 h, ether (200 ml) was added, the mixture was filtered through a sintered glass funnel and the pyridinium.HCl salt collected was washed with ether (2 x 50 ml). The filtrate was evaporated at reduced pressure. The residue was dissolved in ether (200 ml); the solution was washed with 1 N HCl (2 x 100 ml), aqueous 5% $NaHCO_3$ (1 x 100 ml), aqueous saturated NaCl (1 x 100 ml), dried (Na_2SO_4), filtered, and evaporated at reduced pressure. The residue was chromatographed on aluminum oxide (Woelm neutral, 150 g) and fractions (20 ml) were collected automatically and analyzed by analytical tlc for product composition. A mixture of ether and cyclohexane (1:1) was used as solvent until all of the diester was eluted and then the solvent was changed to chloroform. After combination of appropriate fractions and evaporation of the solvent, 18.4 g (53%) of 58 was obtained as a colorless oil.

^{1}H NMR ($CDCl_3$) δ: 1.80 (m, 12), 2.45 (s, 1, OH), 3.80 (m, 1), 5.04 (m, 1), 7.40 (m, 3), 7.95 (m, 2)

5-Oxocyclooctyl benzoate 59

This oxidation was performed using the method developed by Rao and Filler.[73]

To a solution of $Na_2Cr_2O_7.2H_2O$ (22 g, 74 mmol) in 100 ml of dimethylsulfoxide was added hydroxybenzoate 58 (18.4 g, 74 mmol) in 100 ml of dimethylsulfoxide. The mixture was stirred at 0°C and conc H_2SO_4 (17 ml) was added dropwise at such a rate as to maintain the reaction temperature below 40°C. After the addition was complete, the mixture was heated to 60°C for 30 min, cooled to room temperature and poured onto 500 g of ice. The mixture was extracted with ether (3 x 300 ml). The organic extract was washed with aqueous saturated $NaHCO_3$ (3 x 150 ml), dried (Na_2SO_4), filtered, and evaporated at reduced pressure. The residue was dissolved in ether (100 ml) and the solution was washed with water (3 x 50 ml), aqueous saturated NaCl (1 x 50 ml), dried (Na_2SO_4), filtered, and evaporated at reduced pressure. The residue was crystallized from heptane to give 13.75 g (75%) of 59 as a white solid.

mp 60–61°C

ir (CCl_4) cm^{-1} : 2950 (m), 1720 (s), 1280 (s), 1120 (m)

^1H NMR ($CDCl_3$) δ: 1.95 (m, 8), 2.40 (m, 4), 4.90 (m, 1), 7.45 (m, 3), 8.00 (m, 2)

^{13}C NMR ($CDCl_3$) δ: 22.1, 33.2, 42.1, 74.0, 128.4, 129.6, 130.7, 132.9, 165.8, 215.3

mass spectrum, m/e : 246.1253 (2, $m^+ = C_{15}H_{18}O_3$), 124.0888 (40, $C_8H_{12}O$), 105.0339 (100, C_7H_5O)

5-Oxocyclooct-3-en-1-yl benzoate 60

To a stirred solution of keto-benzoate 59 (9.12 g, 37 mmol) in ethyl acetate (300 ml) was added dropwise a solution of phenylselenium chloride (7.60 g, 40 mmol) in ethyl acetate (60 ml). After 1 h, the mixture was poured into water (100 ml), separated, and the organic extract was washed with aqueous saturated $NaHCO_3$ (50 ml) and water (50 ml). The extract was then added to tetrahydrofuran (250 ml) and while cooling at 5°C, a solution of 30% H_2O_2 (9.6 ml) in tetrahydrofuran (40 ml) was added dropwise. The mixture was allowed to warm slowly over a period of 1 h to room temperature and was stirred for an additional 2 h. A 10% aqueous solution of Na_2CO_3 (100 ml) was added and the layers were separated. The organic phase was washed with aqueous saturated $NaHCO_3$ (100 ml), aqueous saturated NaCl (100 ml), dried (Na_2SO_4), filtered, and evaporated at reduced pressure. The residue was dissolved in hot 98% ethanol (50 ml) and upon cooling overnight at -20°C, 4.3 g (48%) of 60 was obtained as white crystals.

mp 66-67°C.

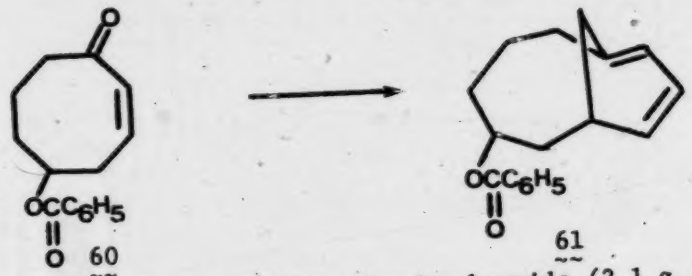
ir (CCl_4) cm^{-1} : 2960 (br), 1720 (s), 1670 (s), 1275 (s), 1120 (s)

^1H NMR ($CDCl_3$) δ: 1.90 (m, 4), 2.85 (m, 4), 5.30 (m, 1), 6.40 (m, 2), 7.45 (m, 3), 8.00 (m, 2)

^{13}C NMR ($CDCl_3$) δ: 18.8, 28.4, 32.8, 41.4, 71.1, 128.5, 129.7, 131.0, 133.2, 137.2, 138.4, 165.8, 202.3

mass spectrum, m/e : 244.1097 (1, $m^+ = C_{15}H_{16}O_3$), 122.0728 (60, $C_8H_{10}O$), 105.0338 (100, C_7H_5O)

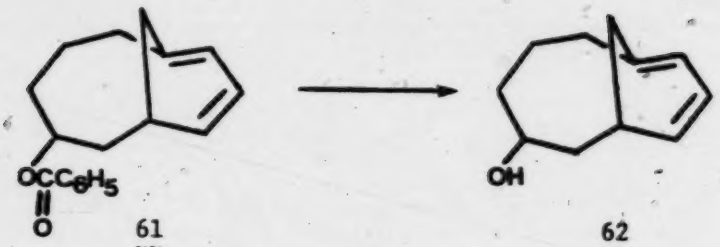
3-Bicyclo[5.3.1]undeca-7,9-dienyl benzoate 61



To a solution of allylphosphonium bromide (2.1 g, 5.5 mmol) in tetrahydrofuran (40 ml) was added potassium *tert*-butoxide (0.57 g, 5.1 mmol) and the mixture was stirred for 3 h at room temperature. A solution of eneone-benzoate 60 (0.8 g, 3.3 mmol) in tetrahydrofuran (2 ml) was added and the mixture was stirred overnight. The mixture was poured into pentane (200 ml) and filtered through a pad of Celite in a sintered glass funnel. The filtrate was washed with water (2 x 100 ml), dried (Na_2SO_4), filtered, and evaporated at reduced pressure. The residue was purified by ptlc (silica gel, ethyl acetate/hexane, 1:3) to give 175 mg (20%) of 61 as a colorless oil.

^1H NMR ($CDCl_3$) δ: 2.0 (br m, 10), 5.0 (br m, 1), 5.85 (m, 2), 6.15 (m, 1), 7.40 (m, 3), 8.00 (m, 2)

Bicyclo[5.3.1]undeca-7,9-diene-3-ol 62.



61 62

To a solution of benzoate 61 (140 mg, 0.52 mmol) in methanol (6 ml) was added a solution of sodium methoxide (0.5 N, 0.2 ml, 0.10 mmol) and the mixture was left stirring overnight. Solid $NaHCO_3$ (100 mg) was added and the mixture was evaporated. The residue was extracted with ethyl acetate (10 ml) and filtered through a pad of Celite in a sintered glass funnel. The solids were washed with ethyl acetate (2 x 25 ml) and the combined filtrate was evaporated at reduced pressure. The residue was purified by ptlc (silica gel, ethyl acetate/hexane, 1:3) to give 49 mg (58%) of 62 as a colorless oil.

ir (neat) cm^{-1} : 3330 (br, s), 3040 (m), 2940 (s), 2850 (m), 1450 (m)

^1H NMR ($CDCl_3$) δ: 2.0 (br m, 11), 3.71 (m, 1), 5.9 (m, 3)

mass spectrum, m/e : 164.1199 (99, $m^+ = C_{11}H_{16}O$), 146.1093 (11, $C_{11}H_{14}$), 135.0807 (70, $C_9H_{11}O$), 105.0338 (100, C_7H_5O)

Bicyclo[5.3.1]undeca-7,9-diene-3-one 63.

62 63

The Collins' oxidation method was used.[77]

To a solution of pyridine (0.3 ml, 3.6 mmol) in dichloromethane (4.5 ml) cooled to 0°C was added with stirring CrO_3 (0.18 g, 1.8 mmol). After 5 min at 0°C, the mixture was allowed to warm to room temperature slowly over 1 h. A solution of alcohol 62 (0.50 mg, 0.30 mmol) in dichloromethane (2 ml) was added. The mixture was stirred for 15 min and was then decanted into a separatory funnel. The reaction residue was extracted and decanted successively with ether (3 x 10 ml). The combined organic phase was washed with cold (5°C) aqueous 5% NaOH (3 x 10 ml), cold aqueous 5% HCl (2 x 10 ml), aqueous saturated NaCl (2 x 10 ml), dried (Na_2SO_4), filtered, and evaporated at reduced pressure to give 31.4 mg (64%) of 63 as a colorless oil.

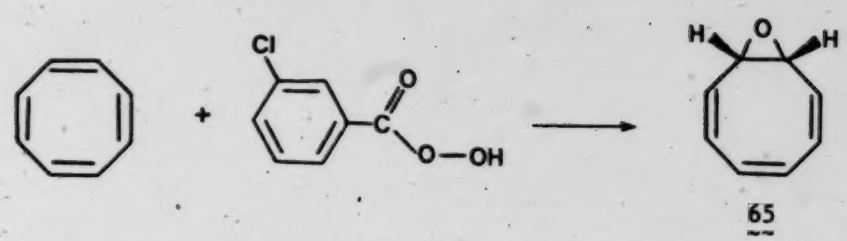
ir (CCl_4) cm^{-1} : 3010 (w), 2950 (m), 1710 (s)

^1H NMR ($CDCl_3$) δ: 2.02 (dd, J=10.0 Hz, J=4.0 Hz, 1), 2.22 (br s, 7), 2.40 (m, 1), 2.64 (m, 2), 5.60 (br d, J=4.0 Hz, 1), 6.05 (m, 2)

^{13}C NMR ($CDCl_3$) δ: 30.1 (t), 32.0 (t), 33.3 (d), 36.0 (t), 43.5 (t), 44.3 (t), 125.0 (d), 126.7 (d), 128.7 (d), 137.3 (s), 209.1 (s)

mass spectrum, m/e : 162.1042 (18, $m^+ = C_{11}H_{14}O$), 104.0625 (100, C_8H_8)

Cyclooctatetraene Oxide 65



65

A modified procedure similar to that of Cope[77] was used.

To a mechanically stirred solution of cyclooctatetraene (52 g, 0.5 mol) in dichloromethane (1 ℓ) cooled to 5°C was added 3-chloroperbenzoic acid (130 g, 0.63 mol) in approximately 20 g portions over a 1 h period. The mixture was allowed to warm to room temperature and stirred for 10 h. The precipitated 3-chlorobenzoic acid was collected by filtration and washed with dichloromethane (2 x 100 ml). The combined filtrate and washings were washed with dilute aqueous $Na_2S_2O_3$ (200 ml), water (200 ml), aqueous saturated $NaHCO_3$ (2 x 200 ml) and aqueous saturated NaCl (200 ml). The organic extract was dried (Na_2SO_4), filtered and evaporated at reduced pressure (room temperature, 20 mm). The residue was distilled through a 10-cm Vigreux column to give 35 g (60%) of 65 (bp 85-90°C, 20 mm).

ir (neat) cm^{-1}: 3000 (s), 2960 (s), 1075 (m), 1010 (s), 900 (m)

^1H NMR ($CDCl_3$) δ: 3.46 (s, 2), 6.00 (m, 6)

^{13}C NMR ($CDCl_3$) δ: 55.32 (d), 125.87 (d), 126.66 (d), 128.12 (d)

Cyclooct-2,4,6-trienone 64

65 64

A modified procedure similar to that of Cope[77] was used.

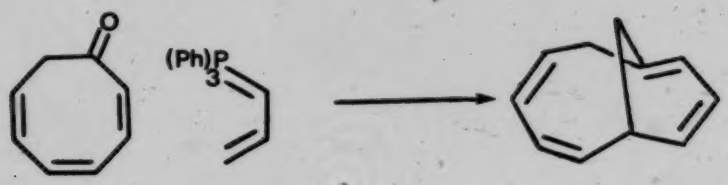
A hexane solution of *n*-butyllithium (1.5 M, 80 ml, 0.12 mol) was added slowly with stirring to a cold (-40°C) solution of diisopropylamine (20 ml, 0.14 mol) in tetrahydrofuran (120 ml). After stirring at -30°C for 30 min, cyclooctatetraene oxide (12 g, 0.10 mol) was added dropwise while maintaining the reaction temperature between -30° and -20°C. After 15 min stirring at -20°C, 3 N H_2SO_4 (100 ml) was added slowly in order that the reaction temperature remained between -10° and 0°C. After the addition the organic layer was separated and washed with aqueous saturated $NaHCO_3$ (50 ml). The combined aqueous phases were further extracted with ether (2 x 100 ml) and washed with saturated $NaHCO_3$ (50 ml). The combined organic extracts were dried (Na_2SO_4), filtered, and the solvent was evaporated at reduced pressure. The residue was distilled through a 12-cm Vigreux column to give 10.5 g (88%) of 64 as a yellow liquid (bp 62-63°C, 2.2 mm).

ir (CCl_4) cm^{-1}: 3020 (w), 2960 (m), 2930 (m), 2870 (w), 1670 (s), 1630 (m)

^1H NMR ($CDCl_3$) δ: 3.04 (d, J=9.0 Hz, 2), 5.80 (m, 1), 6.50 (m, 5)

^{13}C NMR ($CDCl_3$) δ: 43.76 (t), 126.47 (d), 129.76 (d), 130.00 (d), 133.47 (d), 137.00 (d), 138.22 (d), 192.21 (s)

Bicyclo[5.3.1]undeca-2,4,7,9-tetraene 68



64 68

Potassium *tert*-butoxide (1.1 g, 9.8 mmol) was added to a suspension of allylphosphonium bromide (4.0 g, 10.4 mmol) in tetrahydrofuran (50 ml) and the red mixture was stirred at room temperature for 30 min. Cycloocta-2,4,6-trienone (1.2 g, 10 mmol) was added dropwise and the mixture was stirred for 16 h. Ether (25 ml) and aqueous saturated $NaCO_3$ (25 ml) were added and the dark blue mixture was filtered through a pad of Celite. The layers were separated and the aqueous phase was extracted again with ether (25 ml). The combined ether extract was filtered through a short column of silica gel (30 g) and washed with 150 ml of hexane. The filtrate was evaporated to give a yellow oil. Chromatography on silica gel (50 g) with hexane gave 85.4 mg (6%) of 68 as a pale yellow oil.

ir (CCl_4) cm^{-1} : 3040 (m), 3010 (s), 2970 (m), 2900 (s), 2820 (w), 1580 (w), 1425 (m), 710 (s), 690 (s).

^1H NMR ($CDCl_3$) δ: 2.08 (br d, J=14.0 Hz, 1), 2.55 (d, J=14.0 Hz, 1), 2.75 (m, 1), 3.02 (br s, 2), 5.06 (br d, J=12.0 Hz, 1), 5.4-6.2 (m, 6)

^{13}C NMR ($CDCl_3$) δ: 27.7, 32.9, 38.4, 118.0 (d), 122.6 (d), 122.9 (d), 124.2 (d), 125.5 (d), 127.9 (d), 128.7 (d), 136.4 (s, C1).

mass spectrum, m/e : 144.0930 (48, $m^+ = C_{11}H_{12}$), 143.0854 (25, $C_{11}H_{11}$), 129.0699 (100, $C_{10}H_9$), 115.0547 (42, C_9H_7).

Methyl-4-(dimethylphosphinyl)-2-butenoate 72.

$$P(OCH_3)_3 + BrCH_2CH{=}CHCOOCH_3 \longrightarrow \underset{72}{PO(OCH_3)_2CH_2CH{=}CHCOOCH_3}$$

A modified procedure similar to that described by Bohlmann[138] was used. The reaction was conducted in a fume hood as toxic bromomethane is evolved.

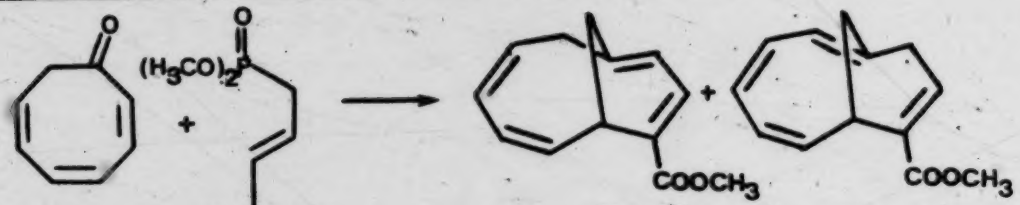
With vigorous stirring, trimethyl phosphite (100 ml, 0.85 mol) was added dropwise to a refluxing solution of methyl 4-bromo-2-butenoate (104.5 g, 0.58 mol) in toluene (100 ml). The mixture was refluxed for 1 h and the undesired volatile components were removed by distillation (bath temperature 110°C, 20-40 mm). The residue was fractionally distilled to give 100 g (84%) of 72 as a clear viscous liquid (bp 118-120°C, 0.1 mm)

ir (neat) cm^{-1}: 3000 (w), 2960 (m), 1730 (s), 1660 (m), 1440 (m), 1330 (m), 1270 (s), 1210 (br), 1150 (br)

^1H NMR ($CDCl_3$) δ: 2.8 (ddd, J=23 Hz, J=8 Hz, J=1.5 Hz, 2, H4), 3.7 (d, J=4 Hz, 6, OCH_3), 4.2 (s, 3, $COOCH_3$), 6.0 (m, 1, H2) 6.72 (m, 1, H3)

10-Methoxycarbonylbicyclo[5.3.1]undeca-2,4,7,9-tetraene 73 and

8-Methoxycarbonylbicyclo[5.3.1]undeca-1,3,5,8-tetraene 74



64 72 73 74

A sodium hydride dispersion in mineral oil (53%, 10 g, 0.22 mol) was washed free of mineral oil by decanting successively with pentane, (2 x 20 ml) and tetrahydrofuran (500 ml) was added. With mechanical stirring, a solution of methyl 4-(dimethylphosphinyl)-2-butenoate (50 g, 0.22 mol) in tetrahydrofuran (30 ml) was added dropwise over 30 min to the cold (-10°C) suspension of sodium hydride. Vigorous gas evolution (H_2) was observed and the mixture was stirred at 0°C for 15 min after the addition was complete. A solution of cycloocta-2,4,6-trienone (20 g, 0.17 mol) in tetrahydrofuran (20 ml) was added dropwise over 15 min and the resulting dark purple mixture was stirred at 0°C for 3 h and then at room temperature overnight. The mixture was cooled (0°C) and diluted with saturated aqueous $NaHCO_3$ (400 ml), stirred for 10 min, and then was extracted with a mixture of hexane and ether (1:1, 3 x 200 ml). The combined organic extracts were dried (Na_2SO_4), filtered, and evaporated (room temperature, 10 mm). The residue was dissolved in benzene (10 ml), filtered through alumina (Woelm neutral, activity I, 20 g) and eluted with 5% ethyl acetate in hexane. The filtrate was evaporated (room temperature, 10 mm) and the residue was chromatographed on alumina (50 g, eluted with 5% ethyl acetate in hexane) to give 8.5 g (25%) of a mixture of 73 and 74 as a pale yellow oil. The two isomers were separated by preparative thin layer chromatography on 10% $AgNO_3$

impregnated silica gel (EM^{R}, silica gel 60).

73

uv (cyclohexane) λ_{max}, log ε: 230 (4.01), 304 (3.74)

ir (neat) cm^{-1} : 3000 (m), 2980 (m), 1700 (s), 1575 (m), 1440 (m), 1270 (br s), 1220 (br m), 1075 (m)

^{1}H NMR ($CDCl_3$) δ: 2.10 (br d, $J_{11a,b}$=14.0 Hz, 1, H11), 2.66 (dd, $J_{11a,b}$=14.0 Hz, J=2.4 Hz, 1, H11), 3.09 (br s, 2, H2), 3.40 (br s, 1, H7), 3.77 (s, 3, CH_3), 5.14 (m, 1), 5.63 (m, 3), 5.89 (m, 1, H10), 7.07 (d, $J_{9,10}$=5.0 Hz, 1, H9)

^{13}C NMR ($CDCl_3$) δ: 28.6 (dd, C11), 33.6 (d, C7), 39.0 (t, C2) 51.9 (q, CH_3), 119.5 (d), 124.3 (d), 124.4 (d), 125.9 (d), 127.3 (d), 131.3 (s), 135.0 (d), 145.8 (s), 168.2 (s, $\underline{C}OOCH_3$)

mass spectrum, m/e: 202.0993 (40, $m^+ = C_{13}H_{14}O_2$), 143.0860 (100, $C_{11}H_{11}$), 141.0703 (31, $C_{11}H_9$), 128.0626 (66, $C_{10}H_8$), 115.0547 (29, C_9H_7).

74

uv (cyclohexane) λ_{max}, log ε: 206 (4.39), 255 (3.32)

ir (neat) cm^{-1} : 2995 (m), 2940 (m), 2905 (m), 2850 (m), 1710 (s), 1630 (m), 1240 (s), 1220 (s), 1090 (s), 1050 (s), 760 (s)

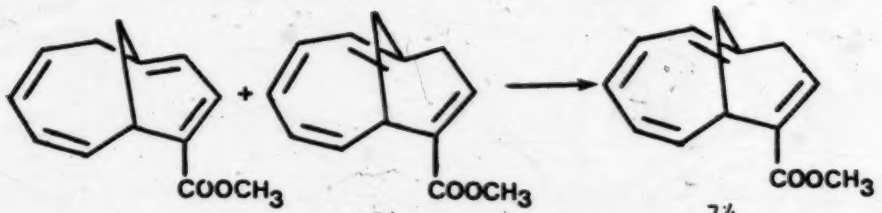
^{1}H NMR ($CDCl_3$) δ: 1.78 (dd, $J_{11a,b}$=11.0 Hz, J=4.0 Hz, 1, H11), 2.98 (m, 3, H10, H11), 3.77 (s, 3, CH_3), 3.84 (m, 1, H7), 5.88 (m, 5), 7.22 (m, 1, H9)

^{13}C NMR ($CDCl_3$) δ: 30.2 (dd, C11), 37.3 (t, C10), 40.8 (d, C7), 51.7 (q, CH_3), 121.5 (d), 122.7 (d), 126.8 (d), 127.2

(d), 134.0 (d), 134.5 (s), 141.5 (d), 142.4 (s), 167.2 (s, $\underline{C}OOCH_3$)

mass spectrum, m/e : 202.0987 (38, $m^+ = C_{13}H_{14}O_2$), 143.0856 (100, $C_{11}H_{11}$), 142.0768 (40, $C_{11}H_{10}$), 141.0702 (67, $C_{11}H_9$), 128.0624 (96, $C_{10}H_8$), 115.0547 (63, C_9H_7)

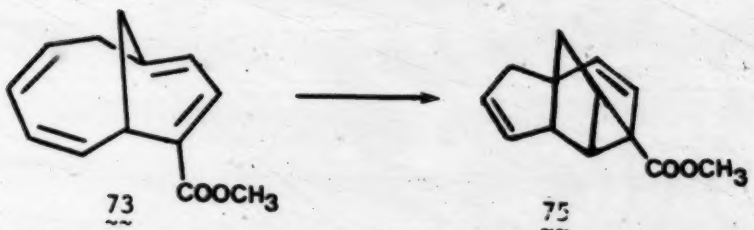
Base Isomerization to 74.



73 74 74

A hexane solution of *n*-butyllithium (1.5 M, 0.73 ml, 1.1 mmol) was added to a solution of diisopropylamine (125 mg, 1.2 mmol) in tetrahydrofuran (5 ml) at -78°C. To this solution was added dropwise a solution of a mixture of the isomeric esters (73:74 = 6:4, 90 mg, in tetrahydrofuran (1 ml). A dark red solution formed which was stirred at -78°C for 1 h. Acetic acid (100 µl) was added and the mixture was allowed to warm to 0°C then poured into cold 0.5 N HCl (20 ml) and extracted with ether (2 x 25 ml). The organic extract was washed with aqueous saturated NaCl (25 ml), dried (Na_2SO_4), filtered, and evaporated at reduced pressure to give 85 mg (95%) of 74 as a colorless oil.

Methoxycarbonyltetracyclo[3.2.1.$0^{2,9}$.$0^{3,7}$]undeca-4,10-diene 75.



73 75

A solution of ester 73 (200 mg, 1.0 mmol) in benzene (5 ml) was refluxed for 16 h. The solvent was evaporated at reduced pressure to give a quantitative yield of quadracyclic ester 75.

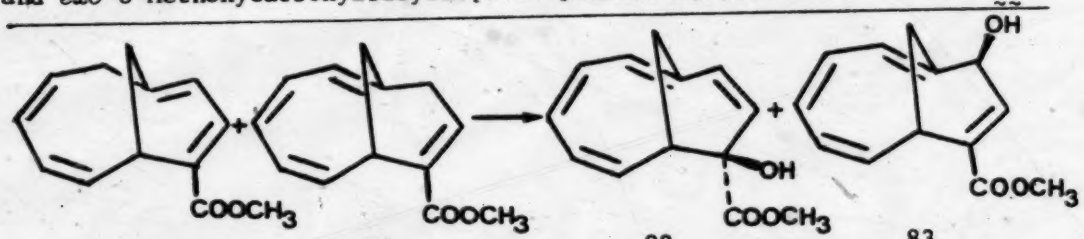
ir ($CHCl_3$) cm^{-1} : 3030 (br, w), 2960 (w), 2930 (w), 2850 (w), 1725 (s), 1440 (m), 1325 (m), 1300 (m), 1290 (m), 1255 (m), 1130 (m)

^1H NMR ($CDCl_3$) δ: 0.75 (d, J=11.0 Hz, 1), 1.76 (dd, J=11.0 Hz, J=2.0 Hz, 1), 1.94 (m, 1), 2.19 (m, 2), 2.35 (m, 2), 3.67 (s, 3), 5.65 (m, 2), 6.18, 6.30 (ABq, 2)

^{13}C NMR (acetone-d_6) δ: 28.2 (d), 28.9 (d), 31.1 (s), 33.8 (dd), 38.1 (t), 50.2 (s), 51.8 (q), 55.4 (d), 121.0 (d), 130.3 (d), 132.1 (d), 133.3 (d), 172.5 (s)

mass spectrum m/e : 202.1000 (55, $m^+ = C_{13}H_{14}O_2$), 143.0860 (100, $C_{11}H_{11}$), 141.0708 (38, $C_{11}H_9$), 128.0626 (72, $C_{10}H_8$)

exo-8-Methoxycarbonylbicyclo[5.3.1]undeca-1,3,5,9-tetraene-8-ol 82
and *exo*-8-Methoxycarbonylbicyclo[5.3.1]undeca-1,3,5,8-tetraene-8-ol 83.



73 74 82 83

A hexane solution of *n*-butyllithium (1.5 M, 3.4 ml, 5.1 mmol) was added slowly to a stirred solution of diisopropylamine (0.75 ml, 5.35 mmol) in tetrahydrofuran (50 ml) cooled to -78°C. The solution was warmed to -40°C for 15 min, cooled again to -78°C, and a solution of isomers 73 and 74 (1.0 g, 4.95 mmol) in tetrahydrofuran (5 ml) was added dropwise. The resulting dark orange-red solution was stirred at -78°C for 1 h after which dry oxygen gas was bubbled into the mixture through a sintered glass gas dispersion tube for 45 min. The cooling bath was removed and at -50°C, 4 N HCl (2 ml) was added followed immediately by triethyl phosphite (5 ml, 24 mmol). The mixture was stirred for 30 min at 0°C and then poured into ice cold water (50 ml) and extracted with ether (2 x 50 ml). The combined ether extracts were washed with water (2 x 50 ml), aqueous saturated $NaHCO_3$ (50 ml), aqueous saturated NaCl (50 ml), dried (Na_2SO_4), filtered, and evaporated to give 2.2 g of yellow oil. This crude product was chromatographed and the impurities eluted first followed by 350 mg (32%) of 82 and 480 mg (44%) of 83. Crystallization of the first fraction from 20% ether in hexane gave 82.

mp 76-77°C

uv (cyclohexane λ_{max}, log ε: 200 (4.37), 288 (3.46)

ir ($CHCl_3$) cm^{-1} : 3530 (br), 3010 (m), 2880 (w), 1730 (s), 1440 (m), 1300 (m), 1260 (s), 1225 (br s), 1090 (m)

^1H NMR ($CDCl_3$) δ: 2.43 (br d, $J_{11a,b}$=13.0 Hz, 1, H11), 3.08 (m, 2, H11, H7), 3.29 (s, 1, OH), 3.77 (s, 3, CH_3), 5.38 (d, $J_{9,10}$=10.0 Hz, 1, H10), 5.96 (m, 4H), 6.66 (d, $J_{9,10}$= 10.0 Hz, 1, H9)

^{13}C NMR ($CDCl_3$) δ: 27.4 (t, C11), 50.3 (d, C7), 52.7 (q, CH_3), 78.1 (s, C8), 121.8 (d, C10), 124.4 (d), 127.2 (d), 128.8 (d), 128.9 (d), 131.4 (d), 133.1 (d, C9), 140.0 (s, C1), 174.5 (s, $\underline{C}OOCH_3$)

mass spectrum, m/e : 2.8.0946 (37, $m^+ = C_{13}H_{14}O_3$), 159.0809 (100, $C_{11}H_{11}O$), 158.0732 (52, $C_{11}H_{10}O$), 149.0239 (41, $C_8H_5O_3$), 141.0703 (40, $C_{11}H_9$), 129.0701 (64, $C_{10}H_9$), 115.0546 (52, C_9H_7), 91.0547 (45, C_7H_7)

Crystallization of the second fraction from 20% ether in hexane gave 83.

mp 93-94°C

uv (cyclohexane) λ_{max}, log ε: 204 (4.23), sh278 (3.03)

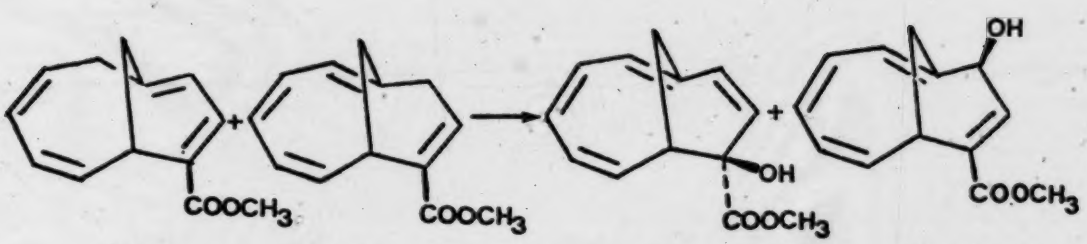
ir ($CHCl_3$) cm^{-1} : 3600 (m), 3420 (br), 3000 (m), 2980 (m), 2950 (m), 2870 (m), 1720 (s), 1630 (w), 1435 (m), 1250 (br s), 1090 (m), 1045 (m), 1010 (m)

^1H NMR ($CDCl_3$) δ: 2.24 (dd, $J_{11a,b}$=11.5 Hz, J=4.5 Hz, 1, H11), 2.41 (s, 1, OH), 2.88 (dd, $J_{11a,b}$=11.5 Hz, J=1.0 Hz, 1, H11), 3.78 (s, 3, CH_3), 3.84 (m, 1, H7), 4.58 (d, $J_{9,10}$=5.0 Hz, 1, H10), 5.86 (m, 5), 7.18 (dd, $J_{9,10}$= 5.0 Hz, J=1.0 Hz, 1, H9)

^{13}C NMR ($CDCl_3$) δ: 25.4 (t, C11), 41.6 (d, C7), 52.1 (q, CH_3), 69.9 (d, C10), 123.4 (d), 124.3 (d), 126.7 (d), 127.4 (d), 133.7 (d), 138.3 (s), 140.2 (d, C9), 142.7 (s), 167.1 (s, $\underline{C}OOCH_3$)

mass spectrum, m/e : 218.0941 (67, $m^+ = C_{13}H_{14}O_3$), 186.0680 (44, $C_{12}H_{10}O_2$), 159.0804 (83, $C_{11}H_{11}O$), 158.0726 (71, $C_{11}H_{10}O$), 157.0650 (49, $C_{11}H_9O$), 141.0704 (54, $C_{11}H_9$), 131.0855 (40, $C_{10}H_{11}$), 129.0699 (100, $C_{10}H_9$), 128.0621 (51, $C_{10}H_8$), 115.0548 (68, C_9H_7), 91.0547 (58, C_7H_7)

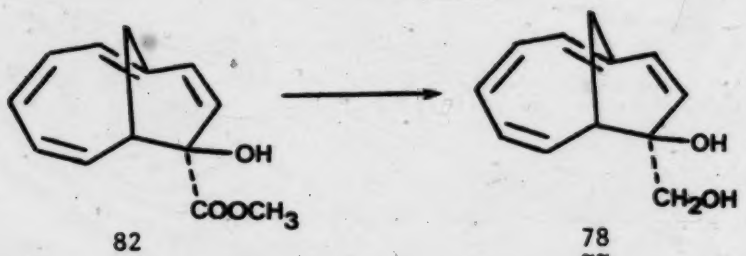
Alternative Hydroxylation with MoO_5.HMPA.pyr.



73 74 82 83

A hexane solution of *n*-butyllithium (1.5 M, 10.7 ml, 16.0 mmol) was added to a stirred solution of diisopropylamine (2.8 ml, 20.0 mmol) in tetrahydrofuran (50 ml) cooled to -78°C. The mixture was warmed to -40°C for 15 min, cooled again to -78°C and a solution of isomers 73 and 74 (3.0 g, 15 mmol) in tetrahydrofuran (10 ml) was added dropwise. The resulting dark orange-red solution was stirred at -78°C for 1 h after which MoO_5.HMPA.pyr (7.0 g. 16 mmol) was added in one portion. The mixture was stirred at -78°C for 1 hr and then allowed to warm to 0°C over 1 h. Water (10 ml) was added and the mixture was poured into ether (100 ml) and 5% aqueous Na_2CO_3 (50 ml). The organic phase was separated and the aqueous phase further extracted with ether (50ml). The combined organic extracts were washed with 5% aqueous HCl (2 x 50 ml), aqueous saturated $NaHCO_3$ (50 ml), aqueous saturated NaCl (50 ml), dried (Na_2SO_4), filtered, and evaporated at reduced pressure to give an orange oil. Chromatography of this crude product on silica gel (200 g) with automatic collection of 20 ml fractions and elution with 10% ether in hexane (2 ℓ), 20% ether in hexane (1 ℓ), and 30% ether in hexane (1 ℓ) resulted in 1.3 g (40%) of 82 in fractions 110-150 and 0.5 g (15%) of 83 in fractions 200-250.

8-Hydroxymethylbicyclo[5.3.1]undeca-1,3,5,9-tetraene-8-ol 78.



82 78

A solution of hydroxy-ester 82 (1.08 g, 4.95 mmol) in ether (15 ml) was added dropwise with stirring to a tetrahydrofuran solution of $LiAlH_4$ (1.2 M, 15 ml, 18.0 mmol) cooled at -5°C. The mixture was stirred for 2 h at room temperature and then was cooled to 0°C after which aqueous saturated ether (100 ml) was slowly added. After 30 min further stirring, Celite filter aid (1.0 g) was added and the mixture was filtered through a pad of Celite in a sintered glass funnel. The solid residue was washed with ether (4 x 50 ml) and the combined filtrate was dried (Na_2SO_4), filtered, and evaporated at reduced pressure to give 830 mg (87%) of 78 as a colorless oil. Crystallization was effected from 20% ether in hexane.

mp 94-94.5°C

ir ($CHCl_3$) cm^{-1} : 3600 (br s), 3420 (br s), 3000 (s), 2930 (m), 2880 (s), 1600 (w), 1050 (br), 1000 (s)

^1H NMR ($CDCl_3$) δ: 2.26 (dd, $J_{11a,b}$=13.0 Hz, J=3.5 Hz, 1, H11), 3.08 (m, 4, H7, H11, two OH), 3.57, 3.65 (AB, J=11.0 Hz, 2, CH_2OH), 5.24 (d, J=10.0 Hz, 1), 6.00 (m, 5), 6.56 (d, J=10.0 Hz, 1)

^{13}C NMR ($CDCl_3$) δ: 27.51 (t, C11), 46.5 (d, C7), 67.00 (t, CH_2OH), 75.69 (s, C8), 123.11 (d), 123.81 (d), 126.77 (d), 128.23 (d), 129.26 (d), 132.71 (d), 133.14 (d),

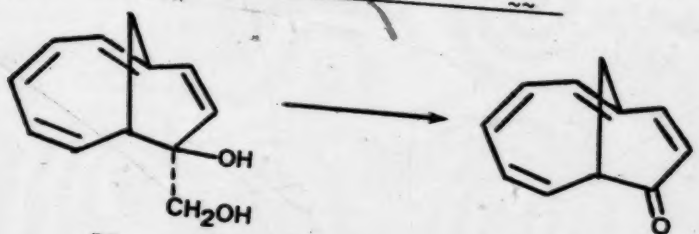
141.72 (s, Cl)

mass spectrum, m/e : 190.0992 (88, $m^+ = C_{12}H_{14}O_2$), 159.0809 (100, $C_{11}H_{11}O$), 141.0697 (47, $C_{11}H_9$), 131.0859 (69, $C_{10}H_{11}$), 129.0699 (73, $C_{10}H_9$), 128.0622 (54, $C_{10}H_8$), 116.0616 (49, C_9H_8), 115.0542 (74, C_9H_7), 91.0548 (63, C_7H_7)

elemental analysis : for $C_{12}H_{14}O_2$ calc: C 75.76, H 7.42, O 16.82

found: C 75.87, H 7.28, O 16.71

Bicyclo[5.3.1]undeca-1,3,5,9-tetraene-8-one 76.



78 76

With vigorous stirring, $NaIO_4$ (600 mg, 2.8 mmol) was added to a solution of diol 78 (400 mg, 2.1 mmol) in a mixture of dioxane and water (1:1, 20 ml). After 4 h stirring, a mixture of ether and pentane (1:1, 40 ml) was added and the solution was filtered through a pad of Celite filter aid in a sintered glass funnel. The solid residue was washed with a mixture of ether and pentane (1:1, 3 x 20 ml) and the combined filtrates were washed with water (3 x 25 ml), aqueous saturated NaCl (25 ml), dried (Na_2SO_4), filtered, and evaporated (room temperature, 10 mm) to give a yellow oil which solidified upon standing. This crude product was sublimed (40-45°C, 0.1 mm) onto a cold finger (-70°C) to give 250 mg (75%) of 76 as a bright yellow crystalline solid.

mp 72-73°C

uv (cyclohexane) λ_{max}, log ε: 220 (4.19), sh252 (3.77), 318 (3.46), sh390 (2.41)

ir ($CHCl_3$) cm^{-1} : 3000 (m), 2920 (w), 2870 (w), 1660 (s), 1630 (w), 1560 (br), 1160 (m), 855 (m), 830 (m)

^1H NMR ($CDCl_3$) δ: 2.68 (dd, $J_{11a,b}$=12.0 Hz, J=3.0 Hz, 1, H11), 3.50 (m, 2, H7, H11), 5.50 (d, $J_{9,10}$=10.0 Hz, 1, H9), 6.02 (m, 5), 7.38 (br d, $J_{9,10}$=10.0 Hz, 1, H10)

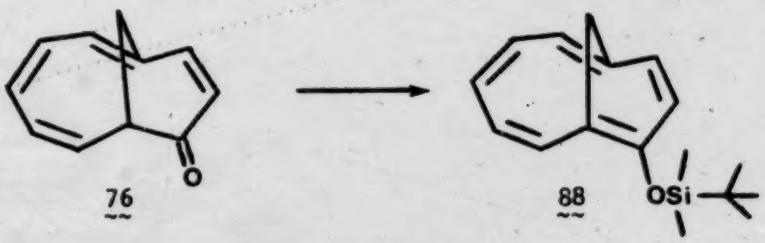
^{13}C NMR ($CDCl_3$) δ: 30.8 (dd, C11), 52.0 (d, C7), 120.6 (d), 127.3 (d), 127.6 (d), 127.8 (d), 130.3 (d), 131.0 (d), 138.3 (s, C1), 147.5 (d), 201.3 (s, C8)

mass spectrum, m/e : 158.0731 (100, $m^+ = C_{11}H_{10}O$), 129.0697 (89, $C_{10}H_9$), 128.0615 (51, $C_{10}H_8$), 115.0548 (61, C_9H_7)

elemental analysis : for $C_{11}H_{10}O$ calc : C 83.51 H 6.37 O 10.11

found : C 83.52 H 6.39 O 10.19

8-*tert*-Butyldimethylsiloxabicyclo[5.3.1]undeca-1,3,5,7,9-pentaene 88.



76 88

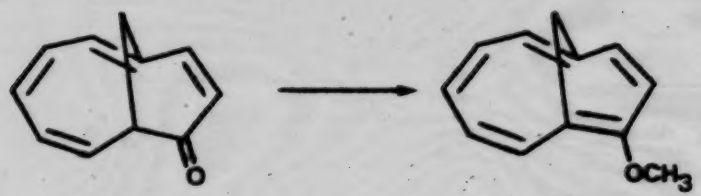
The product of this reaction is air sensitive and therefore all operations were performed under an argon atmosphere and all solvents were purged with argon before use.

A hexane solution of *n*-butyllithium (1.5 M, 0.66 ml, 1.0 mmol) was added dropwise to a solution of diisopropylamine (0.16 ml, 1.14 mmol)

in tetrahydrofuran (9 ml) at -40°C to prepare a 0.10 M solution of lithium diisopropylamide. To a portion of the lithium diisopropylamide solution (0.10 M, 1.3 ml, 0.13 mmol) cooled to -78°C was added dropwise a solution of ketone 76 (20 mg, 0.126 mmol) in tetrahydrofuran (2 ml). A dark brownish-red solution formed and was stirred for 20 min at -78°C. A solution of *tert*-butylchlorodimethylsilane (40 mg, 0.26 mmol) and hexamethylphosphoric triamide (45 µl, 0.25 mmol) in tetrahydrofuran (0.8 ml) was added quickly. The mixture was stirred for 30 min at -78°C and then allowed to warm to room temperature over 1 h. The mixture developed a bright red color during this time and was then poured into cold aqueous saturated NaCl (10 ml) and extracted with pentane. The organic extract was washed with cold aqueous saturated NaCl (2 x 10 ml), dried (Na_2SO_4), filtered and evaporated (room temperature, 10 mm) to give a red oil which was air sensitive. This crude product was chromatographed on silica gel (activity V, 10 g) with benzene. The visible red band was collected and the solvent was evaporated (room temperature, 10 mm) to give 19 mg (55%) of 88 as a bright red oil.

^{1}H NMR (benzene-d_6) δ: -0.62 (dd, J=10.0 Hz, J=2.0 Hz, 1), -0.30 (d, J=10.0 Hz, 1), 0.21 (s, 3), 0.32 (s, 3), 1.08 (s, 9), 6.20 (d, J=8.0 Hz, 1), 7.05 (m, 3), 7.43 (br d, J= 8.0 Hz, 1), 7.93 (m, 1), 8.07 (m, 1).

8-Methoxybicyclo[5.3.1]undeca-1,3,5,7,9-pentaene 89.



76 89

The product of this reaction is air sensitive and therefore all operations were performed under an argon atmosphere and all solvents were purged with argon before use.

A 50% dispersion of sodium hydride (14 mg, 0.29 mmol) was washed with pentane (3 x 1 ml) and then hexamethylphosphoric triamide (HMPA)(1 ml) was added. A solution of ketone 76 (25 mg, 0.158 mmol) in HMPA (0.5 ml) was added dropwise to the suspension at 0°C. The mixture was stirred for 30 min after which methyl fluorosulfonate (Magic Methyl™) (0.35 mg, 0.3 mmol) was added and the mixture was stirred for an additional 30 min. The initial dark green enolate solution gradually became red. Pentane (5 ml) was added and the mixture was poured into cold 5% aqueous $NaHCO_3$ (10 ml). The mixture was extracted with pentane (2 x 10 ml) and the organic extract was washed with cold H_2O (3 x 10 ml) and cold aqueous saturated NaCl (1 x 10 ml) and dried by filtering through Na_2SO_4. The solvent was evaporated (room temperature, 10 mm) to give 81 mg of a red oil which was air sensitive when neat. (The red color was rapidly lost upon standing in the presence of air). Purification was effected by rapid chromatography through a short column of silica gel (activity V, 10 g) with cyclohexane. The visible red band was collected to give 5 mg (18%) of 89 as a red oil.

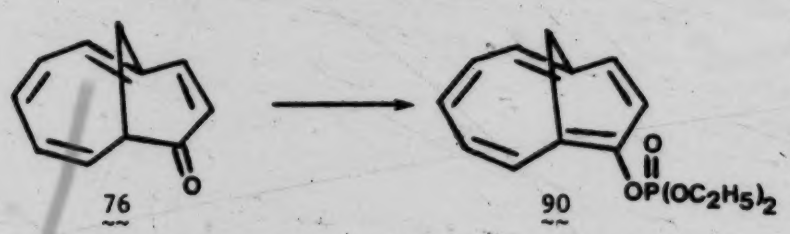
uv (cyclohexane) λ_{max}, log ε: 244 (4.0), 290 (4.1), 355 (3.4), 505 (2.5)

^{1}H NMR (acetone-d_6) δ: -0.34, -0.20 (ABq, $J_{11a,b}$=10.0 Hz, 2, H11), 3.90 (s, 3, OCH_3), 5.85 (d, J=7.0 Hz, 1, H9), 6.95 (m, 3), 7.20 (m, 1), 7.55 (m, 1), 8.06 (m, 1)

^{13}C NMR (acetone-d_6) δ: 34.2 (dd, C11), 57.5 (q, OCH_3), 104.05 (d), 122.6 (d), 123.4 (d), 128.9 (d), 133.7 (d), 138.2 (d), 145.3 (d), 150.4 (s), 154.6 (s), 165.5 (s, C8)

mass spectrum, m/e : 172.0885 (54, $m^+ = C_{12}H_{12}O$), 171.0814 (54, $C_{12}H_{11}O$), 157.0650 (57, $C_{11}H_9O$), 141.0708 (57, $C_{11}H_9$), 128.0623 (74, $C_{10}H_8$).

Bicyclo[5.3.1]undeca-1,3,5,7,9-pentaene-8-yl diethyl phosphate 90.



76 90

To a stirred solution of ketone 76 (50 mg, 0.316 mmol) in tetrahydrofuran (1.5 ml) at -78°C was added dropwise a solution of lithium diisopropylamide (0.1 M, 3.2 ml) (*vide supra*). The mixture was stirred for 15 min and then a solution of diethyl chlorophosphate (71 mg, 0.41 mmol) and hexamethylphosphoric triamide (0.1 ml, 0.56 mmol) in tetrahydrofuran (1 ml) was added. The mixture was stirred for 2 h at -78°C and then was allowed to slowly warm to room temperature over a 1 h period. The red colored solution which developed was poured into cold water (10 ml) and the mixture was extracted with hexane in ethyl acetate (1:2, 10 ml). The organic extract was washed with cold water (3 x 10 ml), aqueous saturated NaCl (10 ml), dried (Na_2SO_4), filtered, and evaporated (room temperature, 2 mm) to give 122 mg of a red oil. The crude product was purified by chromatography on silica gel (activity IV, 20 g) with benzene; the visible red band was collected and the solvent was evaporated (room temperature, 2 mm) to give 75 mg (90%) of 90.

^{1}H NMR (benzene-d_6) δ: -0.96 (dd, J=10.5 Hz, J=2.0 Hz, 1, H11), -0.27 (br d, J=10.5 Hz, 1, H11), 1.15 (br t, J=7.0 Hz, 6), 4.10 (m, 4), 6.85 (d, J=8.5 Hz, 1), 7.03 (m, 3), 7.46 (br d, J=8.5 Hz, 1), 7.62 (m, 1), 8.60 (m, 1).

8,10-Dichlorobicyclo[5.3.1]undeca-1,3,5,8-tetraene 91.

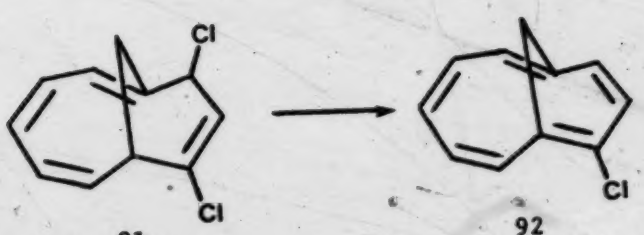
76 91

To a stirred suspension of phosphorus pentachloride (75 mg, 0.36 mmol) in dichloromethane (1 ml) was added ketone 76 (50 mg, 0.31 mmol). The mixture was stirred at room temperature for 4 h, poured into cold aqueous 5% $NaHCO_3$ (10 ml), and extracted with hexane (2 x 10 ml). The organic extract was washed with saturated aqueous NaCl, dried (Na_2SO_4), filtered, and evaporated at reduced pressure to give 60 mg (90%) of a pale yellow oil. This product was used directly in the next reaction.

^1H NMR ($CDCl_3$) δ: 2.57 (dd, J=12.0 Hz, J=4.5 Hz, 1, H11), 2.91 (br d, J=12.0 Hz, 1, H11), 3.41 (br d, 1), 4.90 (dd, J= 4.5 Hz, J=1.0 Hz, 1), 6.0 (m, 6)

mass spectrum , m/e : 212.0159 (12, $m^+ = C_{11}H_{10}Cl_2$), 214.0214 (8, $C_{11}H_{10}Cl_2$), 141.0703 (100, $C_{11}H_9$)

8-Chlorobicyclo[5.3.1]undeca-1,3,5,7,9-pentaene 92.

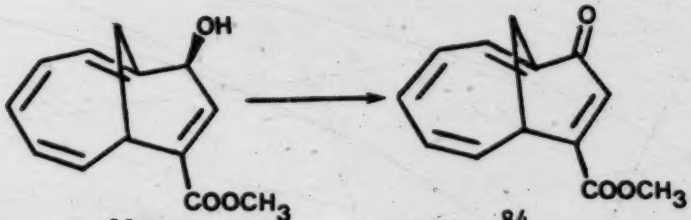


91 92

To a stirred solution of dichloro-compound 91 (40 mg, 0.19 mmol) in tetrahydrofuran (2 ml) at -78°C was added dropwise a solution of lithium diisopropylamide (0.10 M, 2.2 ml, 0.22 mmol) in tetrahydrofuran. The mixture was allowed to warm slowly to 10°C over 1 h and was then poured into cold water (10 ml) and extracted with hexane (2 x 10 ml). The organic extract was washed with cold saturated aqueous NaCl, dried (Na_2SO_4), filtered, and evaporated (room temperature, 10 mm) to give 40 mg of an orange oil which contained about 10% of the desired product 92 by ^1H NMR analysis. Attempted purification by chromatography on silica gel (activity IV, 20 g) with benzene led to decomposition.

^1H NMR (benzene-d_6) δ: -0.99 (dd, J=10.0 Hz, J=2.0 Hz, 1, H11), -0.37 (br d, J=10.0 Hz, 1, H11), 6.40 (d, J=8.0 Hz, 1), 7.0 (m, 3), 7.27 (br d, J=8.0 Hz, 1), 7.54 (m, 1), 8.22 (m, 1)

8-Methoxycarbonylbicyclo[5.3.1]undeca-1,3,5,8-tetraene-10-one 84



83 84

To a vigorously stirred solution of hydroxy-ester 83 (345 mg, 1.58 mmol) in pentane (75 ml) was added activated manganese dioxide (Winthrop Laboratories, 1.50 g, 17 mmol). After stirring for 24 h at room temperature, a mixture of ether and pentane (1:1, 50 ml) and Celite (1.0 g) was added. The mixture was filtered through a pad of Celite in a sintered glass funnel and the solids were washed with a mixture of ether and pentane (1:1, 5 x 20 ml). The combined filtrate was evaporated at reduced pressure to give 270 mg (80%) of a pale yellow oil which solidified upon cooling at 5°C overnight. The crude product was sublimed (60°C, 0.1 mm) onto a dry ice-acetone cold finger to give 84 as a pale yellow solid.

mp 63°C

uv (cyclohexane λ_{max}, log ε: 204 (4.35), 235 (4.16), 336 (2.86), sh406 (1.91), sh430 (1.51)

ir ($CHCl_3$) cm^{-1} : 3010 (w), 2960 (w), 1720 (s), 1680 (s), 1635 (m), 1440 (m), 1250 (br s), 1180 (m), 1108 (m), 1046 (m)

^1H NMR ($CDCl_3$) δ: 2.44 (dd, $J_{11a,b}$=12.0 Hz, J=4.0 Hz, 1, H11), 3.38 (dd, $J_{11a,b}$=12.0 Hz, J=2.5 Hz, 1, H11), 3.86 (s, 3, CH_3), 3.94 (m, 1, H7), 5.96 (m, 4), 6.59 (m, 1), 6.94 (s, 1, H9)

^{13}C NMR ($CDCl_3$) δ: 30.5 (dd, C11), 41.4 (d, C7), 52.7 (q, CH_3), 124.9 (d), 126.8 (d), 129.1 (d), 131.1 (d), 132.9 (d), 135.7 (d), 140.1 (s), 151.1 (s), 166.5 (s, $\underline{C}OOCH_3$), 191.8 (s, C10)

mass spectrum, m/e : 216.0789 (39, $M^+ = C_{13}H_{12}O_3$), 149.0239 (43, $C_8H_5O_3$), 129.0700 (100, $C_{10}H_9$), 128.0624 (79, $C_{10}H_8$), 57.0722 (43, C_4H_9)

elemental analysis : for $C_{13}H_{12}O_3$ calc : C 72.21 H 5.59 O 22.20
found : C 72.17 H 5.65 O 22.18

8-Methoxycarbonyl-10-methoxybicyclo[5.3.1]undeca-1,3,5,7,9-pentaene 93.

84 93

A 50% oil dispersion of sodium hydride (50 mg, 1.0 mmol) was washed with pentane (3 x 5 ml) and then hexamethylphosphoric triamide (HMPA) (3 ml) was added. A solution of the keto-ester 84 (200 mg, 0.93 mmol) in HMPA (1 ml) was added dropwise to the stirred suspension at 0°C. After stirring for 1 h at room temperature, methyl fluorosulfonate (Magic Methyl^{TM}) (150 mg, 1.28 mmol) was added and the mixture was stirred at room temperature for 1 h. A mixture of ether and pentane (1:1, 20 ml) was added and the mixture was then poured into cold 5% aqueous $NaHCO_3$ (20 ml). The mixture was extracted with ether-pentane (1:1, 50 ml) and the organic extract was washed with saturated aqueous

NaCl (3 x 50 ml), dried by filtering through Na_2SO_4 and the solvent was evaporated at reduced pressure (room temperature, 10 mm) to give 43 mg of a red oil. This crude product was purified by chromatography on a short column of silica gel (activity V, 20 g) with cyclohexane. The visible red band was collected and the solvent evaporated at reduced pressure to give 35 mg (16%) of 93 as a red oil.

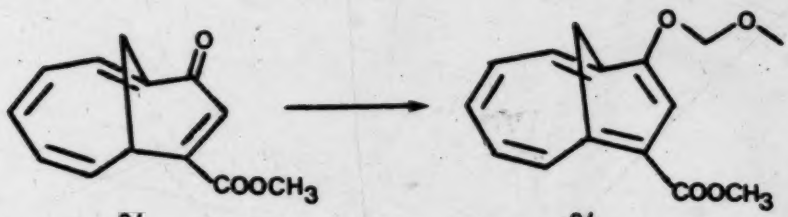
uv (cyclohexane) λ_{max}, log ε: 248 (4.8), 294 (4.6), 375 (4.1), sh500 (3.1)

^{1}H NMR (acetone-d_6) δ: -0.41 (d, $J_{11a,b}$=10.0 Hz, 1, H11), 0.36 (d, $J_{11a,b}$ = 10.0 Hz, 1, H11), 3.86 (s, 3, OCH_3), 3.93 (s, 3, $COOCH_3$), 6.41 (s, 1, H9), 7.14 (m, 3), 7.56 (m, 1), 8.86 (m, 1)

^{13}C NMR (acetone-d_6) δ: 35.8 (dd, C11), 52.0 (q), 56.8 (q), 102.1 (d), 126.2 (d), 126.8 (d), 129.2 (d), 132.1 (s), 136.9 (d), 146.9 (d), 147.1 (s), 150.3 (s), 163.9 (s), 166.5 (s)

mass spectrum, m/e : 230.0934 (84, $m^+ = C_{14}H_{14}O_3$), 229.0863 (34, $C_{14}H_{13}O_3$), 215.0705 (87, $C_{13}H_{11}O_3$), 199.0751 (42, $C_{13}H_{11}O_2$), 156.0571 (44, $C_{11}H_8O$), 155.0499 (43, $C_{11}H_7O$), 141.0703 (20, $C_{11}H_9$), 128.0623 (100, $C_{10}H_8$)

8-Methoxycarbonyl-10-methoxymethyloxabicyclo[5.3.1]undeca-1,3,5,7,9-pentaene 94.

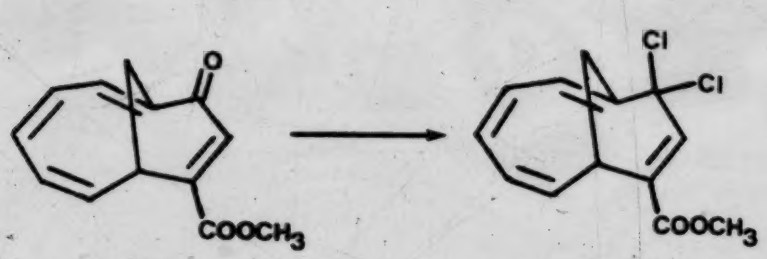


84 94

A 50% oil dispersion of sodium hydride (25 mg, 0.5 mmol) was washed with pentane (3 x 5 ml) and then hexamethylphosphoric triamide (HMPA) (3 ml) was added. A solution of the keto-ester 84 (100 mg, 0.47 mmol) in HMPA (1 ml) was added dropwise to the stirred suspension at 0°C. After stirring for 1 h at room temperature, chloromethyl methyl ether (50 mg, 0.62 mmol) was added. The mixture was stirred at room temperature for 2 h and then cold 5% aqueous $NaHCO_3$ (20 ml) was added. The mixture was extracted with ether-pentane (1:1, 50 ml) and the organic extract was washed with saturated aqueous NaCl (3 x 50 ml), dried by filtering through Na_2SO_4 and the solvent was evaporated (room temperature, 10 mm) to give 105 mg of a red oil. This crude product was purified by chromatography on a short column of silica gel (activity V, 20 g) with cyclohexane. The visible red band was collected and the solvent was evaporated as before to give 80 mg (60%) of 94 .

^1H NMR ($CDCl_3$) δ: -0.70 (d, J=10.5 Hz), 0.12 (d, J=10.5 Hz), 3.56 (s, 3), 3.80 (s, 3), 5.24 (center ABq, J=6.0 Hz, 2), 6.87 (s, 1), 7.20 (m, 3), 7.80 (m, 1), 8.88 (m, 1).

10-Dichloro-8-methoxycarbonylbicyclo[5.3.1]undeca-1,3,5,8-tetraene 95.

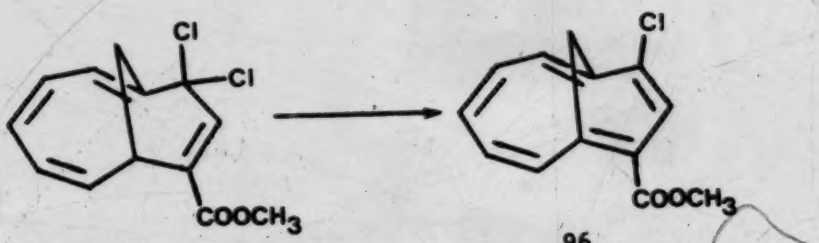


84 95

To a stirred suspension of phosphorus pentachloride (75 mg, 0.36 mmol) in dichloromethane (1 ml) was added keto-ester 84 (50 mg, 0.23 mmol). The mixture was stirred for 4 h at room temperature and was then poured into cold (0°C) aqueous 5% $NaHCO_3$ (10 ml) and extracted with hexane (2 x 10 ml). The organic extract was washed with cold saturated aqueous NaCl, dried (Na_2SO_4), filtered, and evaporated at reduced pressure to give 80 mg of a pale yellow oil. Attempted purification by ptlc on silica gel resulted in decomposition, therefore the mixture was not purified but used directly in the next reaction.

^1H NMR ($CDCl_3$) δ: 2.40 (dd, J=15.0 Hz, J=1.5 Hz, 1, H11), 3.09 (dd, J=15.0 Hz, J=2.5 Hz, 1, H11), 3.50 (br, 1, H7), 3.82 (s, 3, OCH_3), 4.6 (m, 5), 7.00 (s, 1, H9)

10-Chloro-8-methoxycarbonylbicyclo[5.3.1]undeca-1,3,5,7,9-pentaene 96.

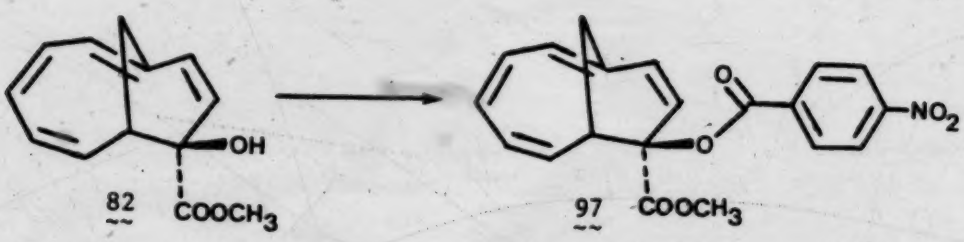


95 96

To a stirred solution of crude dichloroester 95 (70 mg, 0.27 mmol) in tetrahydrofuran (2 ml) at -78°C was added dropwise a tetrahydrofuran solution of lithium diisopropylamide (0.1 M, 2.4 ml. 0.24 mmol). The deep red colored solution which formed was stirred for 1 h at -78°C and was then allowed to warm slowly to room temperature over 2 h. The mixture was poured into ice-water (10 ml) and extracted with hexane (2 x 10 ml). The organic extract was washed with cold aqueous saturated NaCl, dried (Na_2SO_4), filtered, and evaporated at reduced pressure to give 50 mg of crude 96 as a red oil. Attempted purification by chromatography on silica gel (activity IV, 10 g) with benzene resulted in decomposition.

^{1}H NMR (benzene-d_6) δ: -1.2 (d, 1, J=10.5 Hz), -0.22 (br d, 1, J= 10.5 Hz), 7.00 (m, 3), 7.54 (s, 1), 7.83 (m, 1), 8.62 (m, 1).

8-Methoxycarbonylbicyclo[5.3.1]undeca-1,3,5,9-tetraene-8-yl *p*-nitrobenzoate 97.



82 97

To a stirred solution of hydroxy-ester 82 (300 mg, 1.38 mmol) in pyridine (6 ml) at 5°C was added *p*-nitrobenzoyl chloride (300 mg, 1.62 mmol). After stirring for 1 h at 5°C and 2 h at room temperature the mixture was poured into aqueous saturated $NaHCO_3$ (25 ml) and extracted with a mixture of ether and pentane (1:1, 3 x 50 ml). The combined organic extracts were washed with aqueous saturated $NaHCO_3$, (2 x 25 ml), aqueous saturated NaCl (25 ml), dried (Na_2SO_4), filtered and evaporated at reduced pressure to give 415 mg (80%) of 97 as a white solid. Crystallization from 10% ether in hexane gave white crystals.

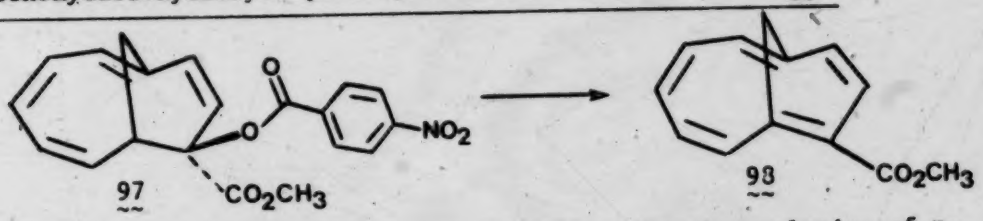
mp 155-156°C

ir ($CHCl_3$) cm^{-1} : 3010 (w), 1745 (s), 1725 (s), 1610 (m), 1530 (s), 1350 (m), 1280 (br s)

^1H NMR ($CDCl_3$) δ: 2.48 (br d, J=12.0 Hz, 1, H11), 3.26 (ddd, J=12.0 Hz, J=3.0 Hz, J=1.5 Hz, 1, H11), 3.58 (m, 1, H7), 3.80 (s, 3, CH_3), 5.36 (br d, J=10.0 Hz, 1, H9), 6.0 (m, 5), 6.73 (d, J=10.0 Hz, 1, H10), 8.25 (q, 4)

mass spectrum, m/e : 367.1058 (2, $m^+ = C_{20}H_{17}NO_6$), 200.0840 (38, $C_{13}H_{12}O_2$), 150.0187 ($C_7H_4NO_3$), 141.0689 (100, $C_{11}H_9$)

8-Methoxycarbonylbicyclo[5.3.1]undeca-1,3,5,7,9-pentaene 98.



In a 100-ml, round-bottomed flask was placed a solution of *p*-nitrobenzoate 96 (100 mg, 0.27 mmol) in benzene (20 ml) and the solvent was evaporated by rapid spinning on a rotary evaporator in order to deposit a thin film of solid 97 on the walls of the flask. The flask was fitted with a dry ice-acetone cold finger and a vacuum take-off. With a pressure of approximately 10-15 mm, the flask was submerged into an oil bath at 160°C for 30 min. An orange and a white sublimate collected on the cold finger. The apparatus was allowed to reach room temperature and then the system was opened under an argon atmosphere. The sublimate was quickly extracted with benzene (20 ml) and the solution was concentrated to about 1 ml by evaporating under vacuum (room temperature, 1 mm). The resulting orange solution was layered on a column of silica gel (activity IV, 30 g) prepared under argon with degassed hexane and eluted with degassed benzene. The visible orange band was collected and the solvent was evaporated (room temperature, 1 mm) to give 30 mg (55%) of 97 as an orange oil.

uv (cyclohexane) λ_{max}, log ε: sh251 (4.1), 266 (4.2), 295 (4.4), 364 (3.9), 480 (2.8)

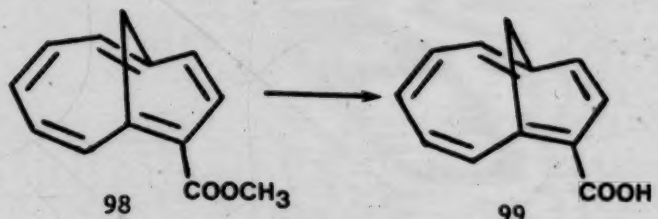
ir ($CHCl_3$) cm^{-1} : 3010 (w), 2960 (w), 1695 (s), 1440 (m), 1250 (br s), 1210 (br s)

^1H NMR (acetone-d_6) δ: -1.27 (dd, J=10.0 Hz, J=1.5 Hz, 1, H11), -0.34 (d, J=10.0 Hz, 1, H11), 3.80 (s, 3, CH_3), 7.50 (m, 5), 8.14 (m, 1), 8.78 (m, 1)

^{13}C NMR (acetone-d_6) δ: 35.3 (dd, C11), 51.5 (q, CH_3), 126.9 (d), 127.9 (d), 128.6 (d), 131.5 (d), 131.9 (d), 134.3 (d), 142.8 (d), 146.1 (d), 155.3 (s), 158.5 (s), 172.1 (s, $\underline{C}OOCH_3$)

mass spectrum, m/e : 200.0838 (34, $m^+ = C_{13}H_{12}O_2$), 141.0709 (100, $C_{11}H_9$)

Bicyclo[5.3.1]undeca-1,3,5,7,9-pentaene-8-carboxylic acid 99.

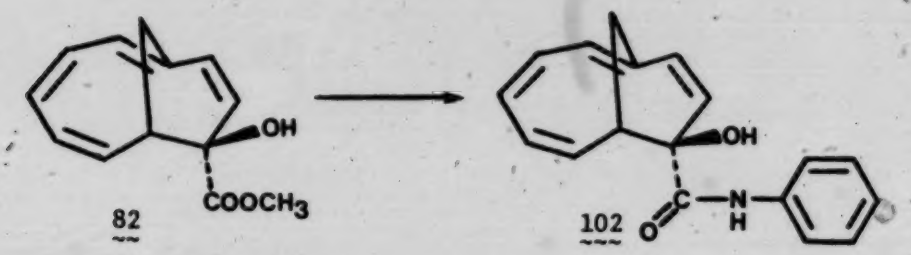


98 99

A solution of 0.5 N KOH in 95% ethanol (1 ml, 0.5 mmol) was added to a solution of ester 98 (48 mg, 0.24 mmol) and the mixture was stirred at 0°C overnight. The solvent was evaporated (room temperature, 1 mm) and the residue was dissolved in ice cold degassed H_2O (20 ml) and extracted with dichloromethane (2 x 10 ml). To the aqueous extract was added dichloromethane (20 ml) and the mixture was acidified carefully to pH 2 using bromophenol blue indicator. The organic phase was separated, dried (Na_2SO_4), filtered, and the solvent was evaporated (room temperature, 1 mm). The residue was chromatographed on silica gel (activity V, 15 g) prepared in hexane and eluted with 20% ethyl acetate in hexane. The visible orange band was collected and the solvent was evaporated as before to give 11 mg (25%) of 99 as an orange oil. Attempted sublimation (0.01 mm, 60°C) led to decomposition. Prolonged exposure of 99 to air (>10 min) led to loss of color.

^1H NMR ($CDCl_3$) δ: -1.21 (dd, J=10 Hz, J=1.5 Hz, 1, H11), -0.30 (d, J=10 Hz, 1, H11), 7.48 (m, 5), 8.12 (m, 1), 8.78 (m, 1).

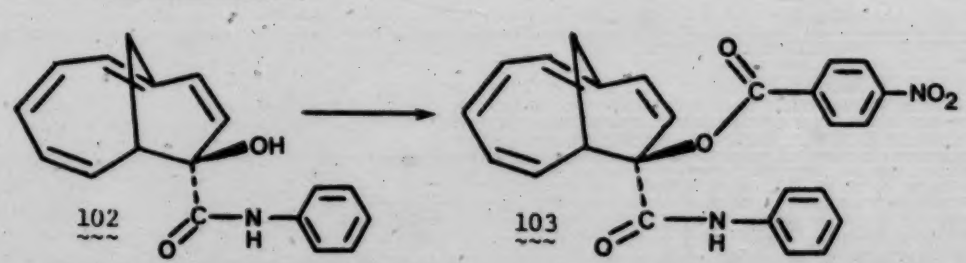
8-Hydroxybicyclo[5.3.1]undeca-1,3,5,9-tetraene-8-yl anilide 102



A hexane solution of *n*-butyllithium (1.6 M, 1.6 ml, 2.6 mmol) was added to a stirred solution of aniline (0.25 ml, 2.7 mmol) in tetrahydrofuran (10 ml) at 0°C, followed by slow addition of a solution of hydroxy-ester 82 (250 mg, 1.15 mmol) in tetrahydrofuran (1 ml). After stirring overnight at room temperature, the solution was poured into an ice cold mixture of 10% aqueous HCl (50 ml) and extracted with ether (2 x 100 ml). The ether extract was washed with aqueous saturated $NaHCO_3$ (50 ml), dried (Na_2SO_4), filtered, and evaporated at reduced pressure to give 160 mg of a white solid. This product was used directly for the next reaction.

^1H NMR ($CDCl_3$) δ: 2.43 (br d, J=12.0 Hz, 1), 3.12 (m, 2), 3.90 (s, 1, OH), 5.44 (d, J=10.0 Hz, 1), 5.90 (m, 5), 6.88 (d, J=10.0 Hz, 1), 7.40 (m, 6).

p-Nitrobenzoate Ester of 102.

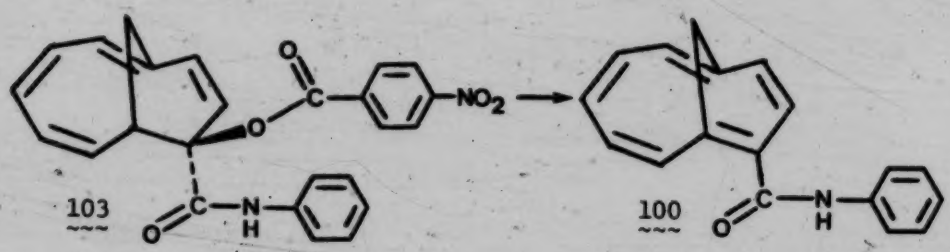


To a solution of anilide 102 (100 mg, 0.35 mmol) in pyridine (2 ml)

was added *p*-nitrobenzoyl chloride (100 mg, 0.54 mmol) and the mixture was stirred overnight. The solvent was evaporated at reduced pressure and the residue was chromatographed (silica gel, 20 g) with 10% ethyl acetate in hexane to give 150 mg (100%) of 103 as an oil. This product was used directly in the next reaction.

H NMR ($CDCl_3$) δ: 2.48 (br d, J=12.0 Hz, 1, H11), 3.26 (dd, J=12.0 Hz, 1, H11), 3.75 (m, 1, H7), 6.0 (m, 7), 7.4 (m, 6), 8.23 (br s, 4).

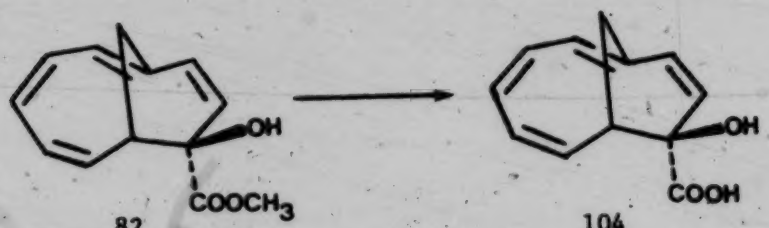
Bicyclo[5.3.1]undeca-1,3,5,7,9-pentaene-8-yl anilide 100.



Pyrolysis of the *p*-nitrobenzoate 103 was carried out in the same manner as for 98 at 300°C (30 mm). The cold finger was extracted with benzene (15 ml), the solution was concentrated at reduced pressure to about 2 ml and then the residue was quickly chromatographed (silica gel, activity V, 20 g) with 10% ethyl acetate in hexane. The visible orange band was collected and the solvent was evaporated to give an amorphous orange solid. Several attempts to form single crystals were unsuccessful.

^{1}H NMR (acetone-d_6) δ: -1.20 (dd, J=10.0 Hz, J=2.0 Hz, 1, H11), -0.30 (d, J=10.0 Hz, 1, H11), 7.45 (m, 8), 7.84 (m, 2), 8.30 (m, 1), 8.58 (m, 1), 9.57 (br s, 1)

8-Hydroxybicyclo[5.3.1]undeca-1,3,5,9-tetraene-8-ylcarboxylic acid 104.

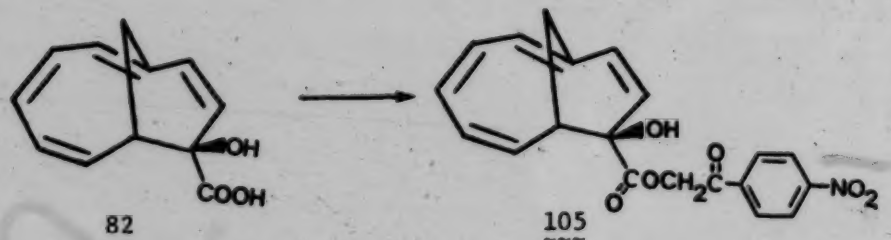


82 104

To a solution of hydroxyester 82 (250 mg, 1.15 mmol) in ether (5 ml) was added a solution of KOH in ethanol (0.5 N, 5 ml, 2.5 mmol) and the mixture was stirred at room temperature. A precipitate slowly appeared and after 5 h water (50 ml) and ether (50 ml) were added. The aqueous layer was separated and acidified at 0°C to pH 1.0 with aqueous 4 M HCl in the presence of an equal volume of ether with stirring. The aqueous phase was extracted with ether (3 x 100 ml) and the combined organic extract was washed with aqueous saturated NaCl (100 ml), dried (Na_2SO_4), filtered, and evaporated to give 200 mg of 104 as a white solid. The crude product was used directly in the next step.

^{1}H NMR (CD_3OD) δ: 2.38 (br d, J=10.0 Hz, 1, H11), 3.10 (m, 2), 5.44 (d, J=10.0 Hz, 1), 5.90 (m, 5), 6.56 (d, J=10.0 Hz, 1).

p-Nitrophenacyl ester of 104.



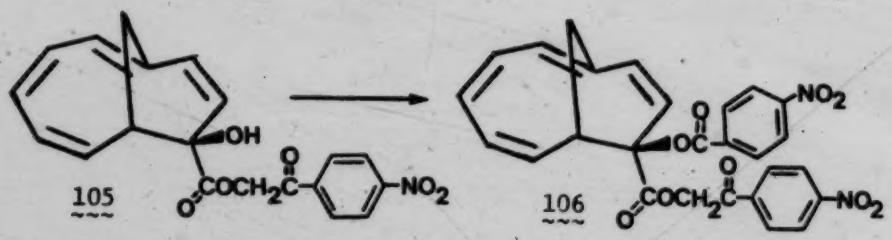
82 105

A solution of the hydroxy acid 82 (200 mg, 1.0 mmole) in water

(2.0 ml) was neutralized by careful titration with an aqueous solution of NaOH (1 M) to pH 6. To this solution was added ethanol (10 ml) and *p*-nitrophenacyl bromide (240 mg, 0.98 mmol). The mixture was refluxed for 2 h and was allowed to cool to room temperature after which time a precipitate had formed. After the addition of aqueous saturated $NaHCO_3$ (50 ml), the mixture was extracted with chloroform (3 x 50 ml) and the organic extract was washed with aqueous saturated NaCl (50 ml), dried (Na_2SO_4), filtered, and evaporated to give 320 mg, (87%) of 105 which was used directly in the next step.

^1H NMR ($CDCl_3$) δ: 2.34 (br d, J=10.0 Hz, 1, H11), 3.20 (m, 3), 5.44 (ABq, J=15.0 Hz, 2), 5.52 (d, J=10.0 Hz, 1), 5.95 (m, 5), 6.68 (d, J=10.0 Hz, 1), 8.20 (m, 4)

p-Nitrobenzoate of 105.



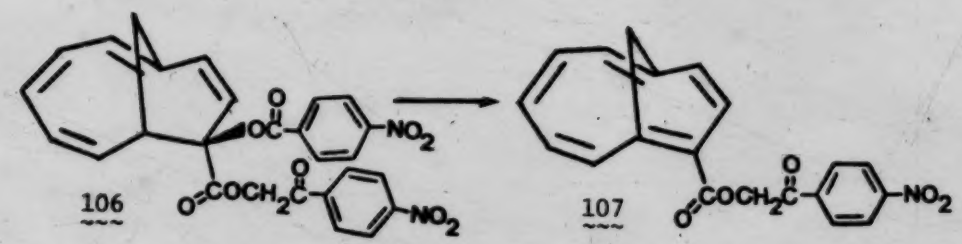
To a solution of phenacyl ester 105 (300 mg, 0.80 mmol) in pyridine (4 ml) was added *p*-nitrobenzoyl chloride (150 mg, 0.81 mmol) and the mixture was stirred at room temperature for 2 h. The solvent was evaporated at reduced pressure. A mixture of water (20 ml), ether (40 ml), and ethyl acetate (20 ml) was added to the residue and the layers were separated. The aqueous phase was further extracted with a mixture of ether and ethyl acetate (1:1, 25 ml). The combined organic extracts were washed with aqueous 1 M HCl (2 x 20 ml), aqueous saturated

NaCl (20 ml), dried (Na_2SO_4), filtered, and evaporated at reduced pressure to give 408 mg (97%) of crude product. Purification was effected by chromatography on silica gel (20 g).

ir ($CHCl_3$) cm^{-1} : 3100 (w), 3000 (br w), 2930 (w), 1750 (s), 1720 (s), 1700 (s), 1600 (s), 1525 (s), 1350 (s), 1280 (s), 1230 (br), 1100 (br)

^1H NMR ($CDCl_3$) δ: 2.54 (br d, J=12.0 Hz, 1, H11), 3.32 (dd, J=12.0 Hz, J=2.0 Hz, 1, H11), 3.70 (br s, 1, H7), 5.60 (ABq, J=15.0 Hz, 2), 6.0 (m, 6), 6.76 (d, J=10.0 Hz, 1, H10), 8.25 (m, 8)

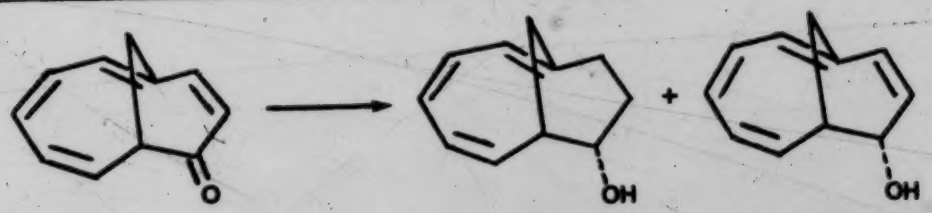
Pyrolysis of *endo*-106 to the *p*-Nitrophenacyl Ester 107.



A solution of phenacyl ester (50 mg, 0.10 mmol) in 25 ml of benzene was evaporated with spinning on a rotovapor to deposit a thin film of oil on the flask. The flask was fitted with a dry ice-acetone cold finger and was evacuated at 5 mm and immersed in an oil bath at 300°C for 5 min. The cold finger was extracted with benzene (50 ml). The solution was concentrated to about 2 ml and chromatographed on silica gel (20 g, activity V) with elution by a mixture of benzene, ethyl acetate, and hexane (2:1:7). The visible yellow-orange band was collected and the solvent was evaporated to give 20 mg (60%) of 107 as a crude orange solid. The product could not be readily purified and

several attempts to prepare single crystals failed.

endo-Bicyclo[5.3.1]undeca-1,3,5,9-tetraene-8-ol 110 and *endo*-Bicyclo[5,3,1]undeca-1,3,5-triene-8-ol 111.



76 111 110

A solution of diisobutylaluminum hydride (1.3 M, 7.1 ml, 9.2 mol) was added dropwise to a cold (-78°C) solution of ketone 76 (815 mg, 5.2 mmol) in ether (75 ml). After stirring for 2 h at -78°C and for 1 h at room temperature, methanol (2 ml) was slowly added. The mixture was stirred vigorously for 1 h, when a white granular precipitate formed which was filtered through a pad of Celite in a sintered glass funnel. The solids were washed with ether (3 x 10 ml) and the combined filtrates were evaporated (room temperature, 10 mm) to give 735 mg of a colorless oil. Chromatography on silica gel (70-200 mesh, 200 g) prepared in hexane and eluted with 10% ether in hexane with automatic collection of 20 ml fractions gave a forerun of 68 mg (8%) of 111 followed by 615 mg (75%) of the desired product 110 as colorless oils.

111

^{1}H NMR ($CDCl_3$) δ: 1.60 (dd, J=12.0 Hz, J=3.0 Hz, 1, H11), 2.20 (m, 3), 2.90 (m, 3), 3.96 (m, 1, H8), 5.90 (m, 5)

^{13}C NMR ($CDCl_3$) δ: 31.2 (dd, C11), 34.9 (t), 37.3 (t), 45.37 (d, C7), 74.9 (d, C8), 120.3 (d), 126.0 (d), 226.8 (d), 127.4 (d), 130.1 (d), 147.7 (s, C1)

110

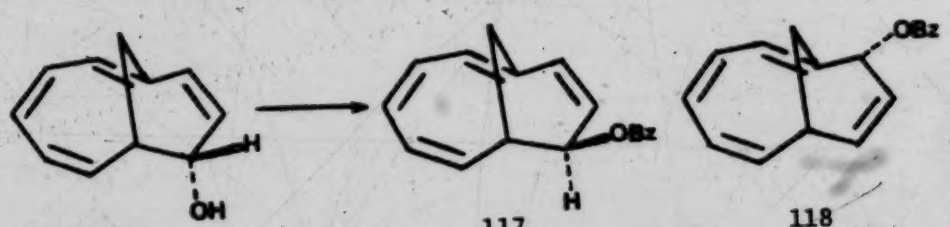
ir ($CHCl_3$) cm^{-1} : 3580 (m), 3410 (br), 2990 (s), 2910 (m), 2850 (s), 1600 (w), 1455 (m), 1060 (s), 1030 (s), 840 (s)

^1H NMR ($CDCl_3$) δ: 2.05 (br d, J=12.0 Hz, 1), 2.38 (s, 1, OH), 3.10 (ddd, J=12.0 Hz, J=4.0 Hz, J=1.8 Hz, 1), 3.40 (m, 1, H7), 4.65 (m, 1, H8), 5.26 (dd, J=10.0 Hz, J=2.0 Hz, 1), 6.00 (m, 5), 6.44 (br d, J=10.0 Hz, 1)

^{13}C NMR ($CDCl_3$) δ: 31.2 (dd, C11), 42.2 (d, C7), 72.3 (d, C8), 122.5 (d), 126.8 (d), 127.2 (d), 128.6 (d), 129.4 (d), 131.0 (d), 131.6 (d), 141.2 (s, C1)

mass spectrum m/e : 160.0888 (45, $m^+ = C_{11}H_{12}O$), 142.0777 (20, $C_{11}H_{10}$), 141.0707 (35, $C_{11}H_9$).

exo-Bicyclo[5.3.1]undeca-1,3,5,9-tetraene-10-yl benzoate 117 and *endo*-Bicyclo[5.3.1]undeca-1,3,5,8-tetraene-10-yl benzoate 118.



110 117 118

To a solution of alcohol 110 (0.514 g, 3.2 mmol), triphenylphosphine (1.70 g, 6.5 mmol) and benzoic acid (0.80 gm, 6.55 mmol) in tetrahydrofuran (20 ml) cooled to -20°C, was added with stirring diethyl azodicarboxylate (1.2 g, 6.89 mmol). The mixture was left at -10°C overnight. The solvent was evaporated and the residue was dissolved in benzene and chromatographed on silica gel (30 g) with benzene. The desired mixture of benzoates was collected in the first 200 ml of eluant. The solvent was evaporated and the residue was carefully chromatographed on silica gel (300 g) with hexane. After eluting with 1 ℓ of hexane, the solvent was gradually changed to 2% ether in hexane. A flow rate of 2.5 ml/min and automatic collection of 20 ml fractions which were analyzed by TLC gave, after combination of appropriate fractions and evaporation of the solvent, 440 mg (52%) of 117, 40 mg (5%) of isomeric mixture, and 190 mg (22%) of 118.

117

^{1}H NMR ($CDCl_3$) δ: 2.26 (br dd, J=12 Hz, J=4 Hz, 1, H11), 3.16 (m, 2, H11, H7), 5.51 (m, 2, H8, H9), 5.96 (m, 5), 6.70 (d, J=9 Hz, 1, H10), 7.47 (m, 3), 8.08 (m, 2)

118

^{1}H NMR ($CDCl_3$) : 2.41 (dd, J=12 Hz, J=5 Hz, 1, H11), 2.99 (d, J=12 Hz,

1, H11), 3.45 (m, 1, H7), 6.0 (m, 7), 7.45 (m, 3), 8.25 (m, 2)

exo-Bicyclo[5.3.1]undeca-1,3,5,9-tetraene-8-ol 116.

117 116

A solution of 0.5 N KOH (7.0 ml, 3.5 mmol) in 95% ethanol was added to a solution of benzoate 117 (440 mg, 1.67 mmol) in ether (10 ml) and stirred at room temperature overnight. The solvent was evaporated (room temperature, 10 mm) and the residue extracted with benzene (3 x 30 ml). The organic extract was washed with 5% aqueous $NaHCO_3$ (50 ml), saturated aqueous NaCl (25 ml), dried (Na_2SO_4), filtered, and evaporated at reduced pressure to give 270 mg (100%) of 116 as a colorless oil. Crystalization from toluene gave white crystals.

mp 77-78°C

uv (cyclohexane) λ_{max}, log ε: 224 (4.22), 288 (3.41)

^{1}H NMR ($CDCl_3$) δ: 2.12 (m, 2), 3.10 (m, 2), 4.11 (d, J=4.5 Hz, 1, H8), 5.48 (dd, J=10 Hz, J=4.5 Hz, 1, H9), 5.95 (m, 5), 6.55 (d, J=10 Hz, 1, H10)

^{13}C NMR ($CDCl_3$) δ: 26.43 (t, C11), 46.07 (d, C7), 72.40 (d, C8), 123.05 (d), 124.02 (d), 126.56 (d), 128.28 (d), 129.36 (d), 132.28 (d), 134.00 (d), 141.07 (s)

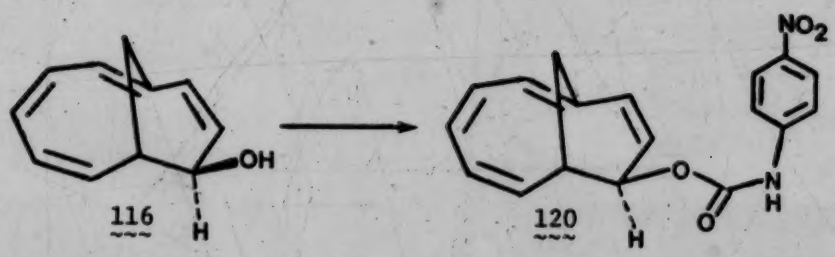
mass spectrum, m/e : 160.0893 (100, $m^+ = C_{11}H_{12}O$), 142.0780 (42, $C_{11}H_{10}$), 141.0707 (57, $C_{11}H_9$), 131.0869 (62, $C_{10}H_{11}$),

129.0707 (69, $C_{10}H_9$), 128.0631 (47, $C_{10}H_8$), 117.0703 (71, C_9H_9), 115.0545 (94, C_9H_7), 91.0547 (83, C_7H_7)

elemental analysis : for $C_{11}H_{12}O$ calc : C 82.46 H 7.55 O 9.99

found : C 82.51 H 7.45 O 10.04

p-Nitrophenylcarbamate of 116.



116 120

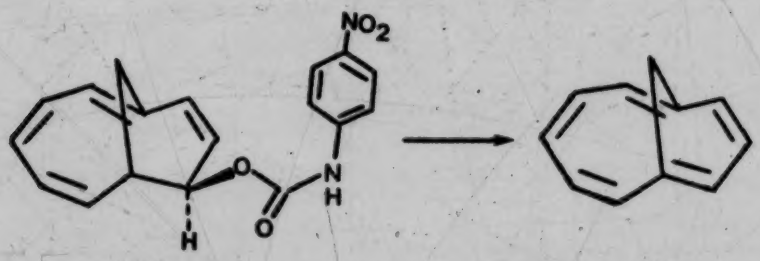
To a stirred solution of alcohol 116 (50 mg, 0.31 mmol) in toluene (2 ml) was added *p*-nitrophenylisocyanate (100 mg, 0.61 mmol) followed by triethylamine (150 µl) and the mixture was left overnight. The mixture was filtered and the solids were washed with benzene (4 x 10 ml). The filtrate was evaporated at reduced pressure and the residue was chromatographed on a short column of silica gel (70-270 mesh, 20 g) prepared in hexane. Elution with 10% ethyl acetate in hexane gave the pure product in the first 100 ml of eluant. Evaporation of the solvent gave 90 mg (90%) of 120 as a white solid.

mp 152-153°C

uv (cyclohexane) λ_{max}, log ε: 222 (4.53), 298 (4.25)

^{1}H NMR ($CDCl_3$) δ: 2.13 (dd, J=12 Hz, J=4 Hz, 1, H11), 3.10 (m, 2), 5.24 (d, J=4 Hz, 1, H8), 5.46 (dd, J=10 Hz, J=4 Hz, 1, H9), 6.10 (m, 6), 6.68 (d, J=10 Hz, 1, H10), 7.57 (d, J=9 Hz, 2), 8.20 (d, J=9 Hz, 2)

Bicyclo[5.3.1]undeca-1,3,5,7,9-pentaene 19.



120 19

In a 50-ml, round-bottomed flask was placed a solution of carbamate 120 (25 mg, 0.08 mmol) in benzene (10 ml) and the solvent was evaporated with rapid spinning on a rotary evaporator in order to deposit a thin film of solid 120 on the walls of the flask. The flask was fitted with a dry ice-acetone cold finger and a vacuum take-off. At a pressure of 150 mm, the flask was immersed into an oil bath at 300°C. Immediately an orange sublimate appeared on the cold finger. After about two minutes the flask was removed from the oil bath and allowed to cool to room temperature. The following operations were carried out quickly under an argon atmosphere. The cold finger was extracted with pure degassed cyclohexane (∿50 ml), concentrated at reduced pressure (20°C, 10 mm) to a volume of about 2 ml and then quickly chromatographed on silica gel (activity V, 10 g) with cyclohexane. The visible orange band was collected and the solvent was evaporated at reduced pressure (20°C, 10 mm) to give approximately 2 mg (18%) of 19 as an orange oil which was air sensitive and unstable in neat form at room temperature ($T_{\frac{1}{2}}$ decomp = ∿12 h). This compound could be stored at -80°C in pentane solution under argon.

uv (cyclohexane) λ_{max}, log ε: 210 (3.9), 255 (4.0), 282 (4.4), sh297 (3.9), sh303 (3.8), 325 (3.5), 480 (2.5)

270 MHz ^{1}H NMR (2:1 diethyl ether-d_{10} and methylcyclohexane-d_{14}) δ:
-0.95 (dt, $J_{11a,b}$=9.72 Hz, $J_{11a,8,10}$=2.05 Hz, 1, H11b), -0.48 (d, $J_{11a,b}$=9.72 Hz, 1, H11a), 6.86 (t, $J_{8,9,10}$=7.56 Hz, 1, H9), 7.30(m, AB_2, 3, H3, H4, H5) 7.52 (d, $J_{8,9,10}$=7.56 Hz, 2, H8, H10), 8.08 (d, $J_{2,3}$= 8.64 Hz, 2, H2, H6)

^{13}C NMR (acetone-d_6) δ: 34.7 (t, C11), 125.1 (d, C3, C5), 128.7 (d, C4), 130.4 (d, C9), 133.5 (d, C8, C10), 144.6 (d, C2, C6), 161.2 (s, C1, C7).

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Part II

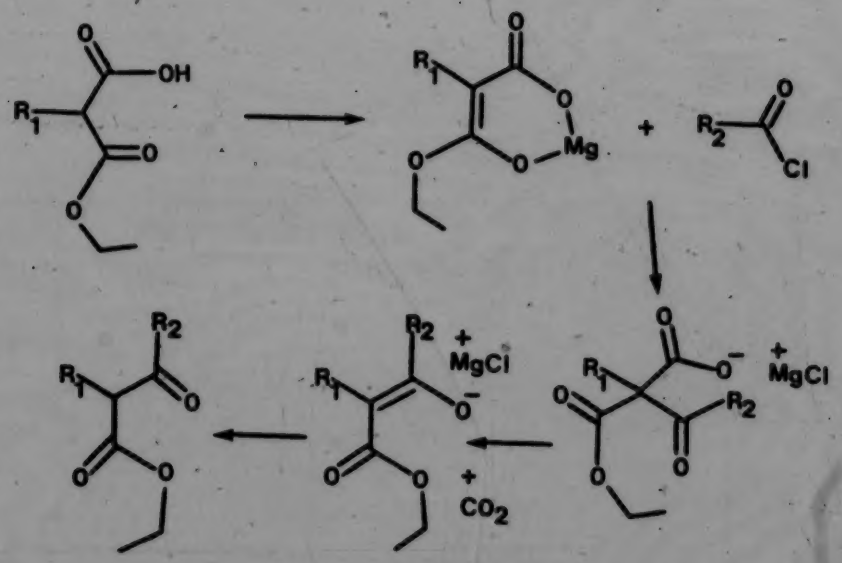
NEW C-ACYLATION

CHAPTER 1

INTRODUCTION

A fundamental endeavour in organic synthesis is to form a carbon-carbon bond under mild and essentially neutral conditions. During the course of investigations directed toward the synthesis of polyoxo-macrolide antibiotics,[1] it became apparent that methods for effecting a mild C-acylation and a stereoselective aldol condensation would greatly facilitate the synthesis of this important class of natural products and related acyclic systems. A satisfactory solution for mild C-acylation will be described which has wide synthetic applicability and patterns to some extent a similar process which occurs in the biosynthesis of fatty acids.

The introduction of an acyl group at carbon is normally performed under strongly basic or acidic conditions.[2] The acid catalyzed conditions are generally useful only for C-acylation of ketones. The development of the reaction of enamines with acid chlorides or acid anhydrides has provided an alternative mild method for C-acylation of ketones.[3] Acylation of esters commonly follows the base catalyzed procedure as illustrated by the classical acetoacetic ester condensation.[4] This reaction is reversible and the equilibrium normally favors the product β-ketoester due to its greater acidity. The C-acylation becomes irreversible when an ester enolate anion is reacted with an acid chloride or acid anhydride but does not always proceed smoothly and is often complicated by O-acylation. Reaction of a magnesium enolate of a malonic half acid ester with an acid chloride overcomes the problem of O-acylation and provides a synthetically useful procedure for the preparation of β-ketoesters as shown.[5]



In the synthesis of complex natural products containing a variety of sensitive functionality, it is not usually possible to carry out a C-acylation reaction unless extensive protection of the sensitive functional groups is invoked. A variety of adequate protecting groups are available[6] and continue to appear, but extensive protection and selective deprotection results in a very lengthy and tedious synthesis of a complex substrate. Thus the need for a neutral, mild method for C-acylation of an ester was evident.

CHAPTER 2

THE BIOSYNTHESIS OF FATTY ACIDS

A clue for a mild method of C-acylation is provided by nature in the biosynthesis of fatty acids and related metabolites.[7] The *de novo* synthesis of fatty acids involves two main processes for the incorporation of acetate via acetyl coenzyme A (CoA) into a long chain fatty acid. The first process involves the carboxylation of acetyl-CoA to form malonyl-CoA by a biotin dependent enzyme and the second process involves the successive addition of C_2-fragments derived from malonyl-CoA to one initial acetyl-CoA primer. The entire sequence of reactions is catalyzed by a multienzyme complex referred to as fatty acid synthetase (FAS). The sequence of reactions involved is shown in Figure 1.

The biosynthesis of fatty acids from malonyl-CoA appears to be a general process which occurs in bacteria, plants, and animals. Lynen and his colleagues[8] provided the first details of the structure and function of the multienzyme complex of yeast over a long series of investigations which eventually led to the isolation of the enzyme system and elucidation of the reaction sequences which have been described. Similar results appeared later for animal, bacterial, and plant systems.[9]

A proposed mechanism for fatty acid biosynthesis formulated by Lynen and coworkers[10] based on their studies with yeast is summarized as follows. One of the protein units of the fatty acid synthase (FAS) complex has the specific purpose of binding the acyl intermediates and is referred to as the acyl carrier protein (ACP).[11] The intermediates involved in this biosynthesis are covalently bound as thiol esters to thiol groups attached to protein. Two types of thiol groups have been

Figure 1. The Sequence of Reactions for Fatty Acid Biosynthesis.

1. Acyl transfer; priming reaction

   a) $CH_3CO\text{-}S\text{-}CoA + HO\text{-}Enzyme \rightleftharpoons CH_3CO\text{-}O\text{-}Enzyme + HSCoA$

   b) $CH_3CO\text{-}O\text{-}Enzyme + HS\text{-}ACP \rightleftharpoons CH_3CO\text{-}S\text{-}ACP + HO\text{-}Enzyme$

2. Transfer to sulfhydryl group of condensing enzyme

   $CH_3CO\text{-}S\text{-}ACP + HS\text{-}Enzyme \rightleftharpoons CH_3CO\text{-}S\text{-}Enzyme + HS\text{-}ACP$

3. Malonyl transfer

   a) $HOOCCH_2CO\text{-}S\text{-}CoA + HO\text{-}Enzyme \rightleftharpoons HOOCCH_2CO\text{-}O\text{-}Enzyme + HSCoA$

   b) $HOOCCH_2CO\text{-}O\text{-}Enzyme + HSACP \rightleftharpoons HOOCCH_2CO\text{-}S\text{-}ACP + HO\text{-}Enzyme$

4. Condensation

   $HOOCCH_2CO\text{-}S\text{-}ACP + CH_3CO\text{-}S\text{-}Enzyme \rightleftharpoons CH_3COCH_2CO\text{-}S\text{-}ACP + CO_2 + HS\text{-}Enzyme$

5. Reduction

   $CH_3COCH_2CO\text{-}S\text{-}ACP + NADPH + H^+ \rightleftharpoons NADP^+ + CH_3CHOHCH_2CO\text{-}S\text{-}ACP$

6. Dehydration

   $CH_3CHOHCH_2CO\text{-}S\text{-}ACP \rightleftharpoons CH_3CH{=}CHCO\text{-}S\text{-}ACP$

7. Reduction

   $CH_3CH{=}CHCO\text{-}S\text{-}ACP + NADPH + H^+ \rightleftharpoons NADP^+ + CH_3CH_2CH_2CO\text{-}S\text{-}ACP$

8. Butyryl transfer

   $CH_3CH_2CH_2CO\text{-}S\text{-}ACP + HS\text{-}Enzyme \rightleftharpoons CH_3CH_2CH_2CO\text{-}S\text{-}Enzyme$

   then back to reaction 4 using butyryl-Enzyme

9. Termination (palmitoyl transfer)

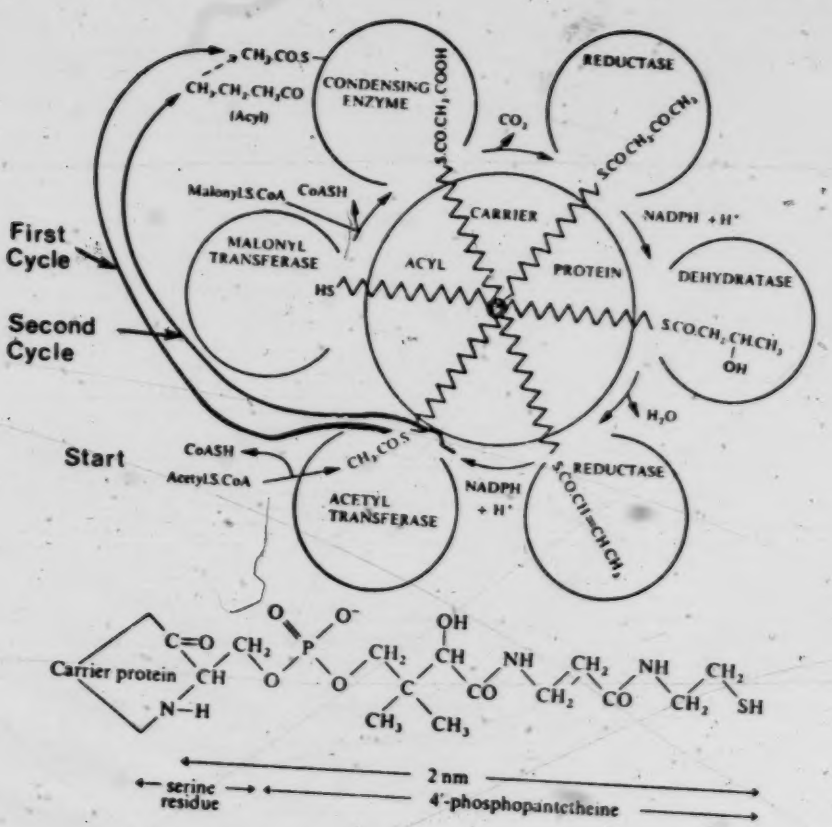
   $CH_3(CH_2)_8CO\text{-}S\text{-}ACP + HS\text{-}CoA \rightleftharpoons CH_3(CH_2)_8CO\text{-}S\text{-}CoA + HS\text{-}ACP$

   i.e., palmitoyl is not transferred to the condensing enzyme.

identified in the FAS complex and are denoted as "central" (S_c) and "peripheral" (S_p) according to their respective location. The S_p-thiol group is a cysteine residue incorporated within a polypeptide chain of the FAS. The S_c-thiol group is attached to the ACP by a 4'-phosphopantetheine unit and the structure of the S_c-thiol group is quite similar in this respect to coenzyme A. The process of fatty acid biosynthesis can be visualized as occurring in a "biological factory" represented by the FAS complex, with a circular assembly line of enzyme active sites. The S_c-thiol group acts as a conveying device carrying and positioning the substrate through the various assembly stages while the S_p-thiol group picks up the substrate at the end of an assembly cycle and also introduces a substrate at the start of the assembly line. A schematic view of the FAS complex and this hypothetical process is shown in Figure 2.[12]

The synthesis of a fatty acid begins with the transfer of the acetyl group from acetyl-CoA to the S_c-thiol group of the FAS. The acetyl-S_c thiol ester is then transferred to the S_p-thiol group which is located near the active site of the condensing enzyme component of the FAS complex. With the acetyl priming sequence complete, the malonyl group of malonyl-CoA is transferred to the S_c-thiol group. The malonyl-S_c-thiol ester is then positioned at the active site of the condensing enzyme and C-acylation occurs accompanied by decarboxylation to give an acetoacetyl S_c-thioester. The ACP next positions this S_c-thiol ester through the active sites of 1) the first reducing enzyme where reduction to β-hydroxybutyryl-S_c-thiol ester occurs, 2) the dehydrating enzyme where crotonyl-S_c-thiol ester is formed and 3) the second reducing

Figure 2. A Hypothetical Scheme for the Function of the Fatty Acid Synthetase Complex.



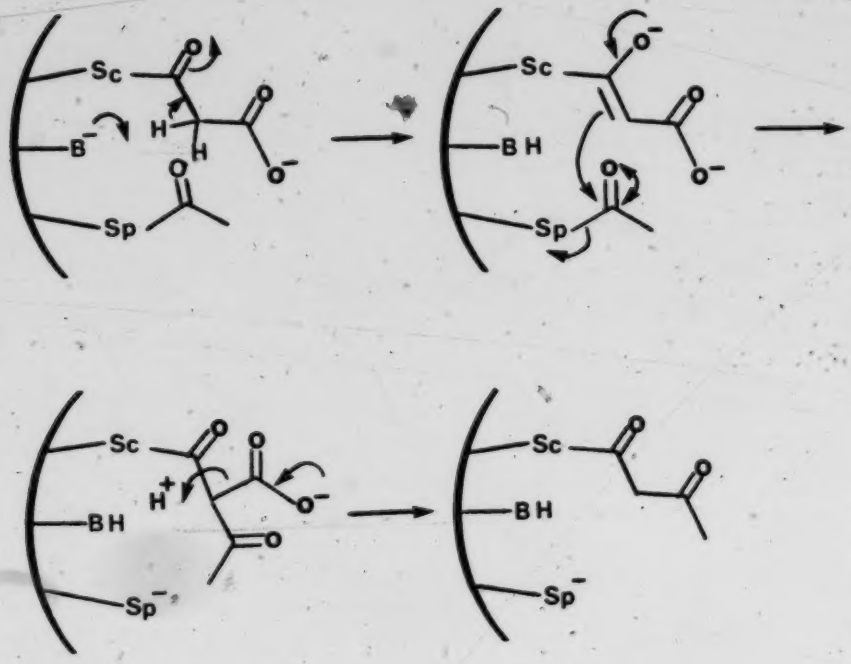
enzyme where butyryl-S_c-thioester is formed. At this stage the butyryl group is transferred to the S_p-thiol group and the cycle commences again. The cycle is repeated in most cases until palmitic- or stearic-S_c-thiol ester is formed which is then released by transfer to co-enzyme A.

The role of malonyl-CoA in the C-acylation reaction is characteristic of the biosynthesis of fatty acids and the concurrent loss of CO_2 makes this condensation reaction irreversible. The actual organic chemistry of the condensation reaction between the acetyl-S_p-thiol ester and the malonyl-S_c-thiol ester is not clearly understood. Lynen and coworkers[10] have proposed two general mechanisms for this C-acylation reaction which are illustrated in Figure 3 and are denoted as 1) the enolate mechanism and 2) the decarboxylation mechanism. In both processes, the carboxyl group of malonyl-S_c-thiol ester plays a key role; in mechanism 1 enolate formation is more accessible due to the increased acidity of malonyl versus acetyl and in mechanism 2 decarboxylation is coupled with C-C bond formation.

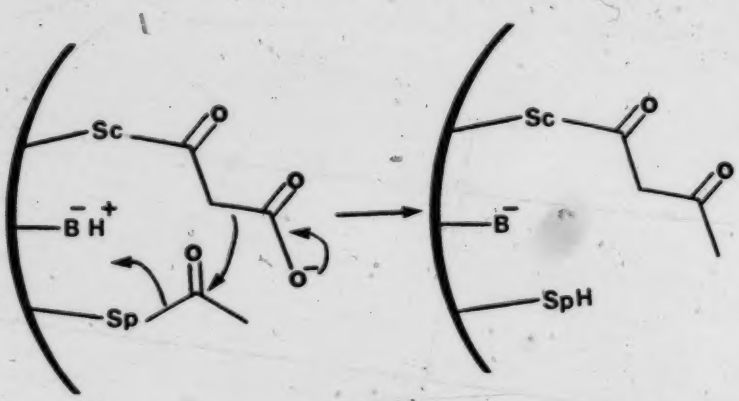
Several experiments have been executed by Lynen and coworkers to determine which of the two general mechanisms more closely fit the biosynthetic process. Previous studies of fatty acid synthesis with purified FAS complex from yeast demonstrated that the condensation reaction was the rate limiting step in the overall process. No difference in the rates of fatty acid synthesis were observed when malonyl-CoA and dideutero malonyl-CoA were compared. Using isolated condensing enzyme from *E.coli*, again, no kinetic isotope effect was found. Furthermore, when ditritiated malonyl-CoA was utilized as the substrate the tritium was retained.[13] These results tend to exclude a mechanism

Figure 3. Proposed Mechanisms for the Biological C-Acylation in Fatty Acid Biosynthesis

1. Enolate Mechanism

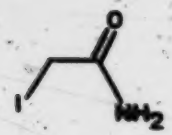


2. Decarboxylation Mechanism

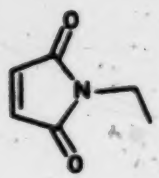


involving a malonyl enolate anion and favor a mechanism where the formation of the new C-C bond is coupled with decarboxylation.

Further studies on the FAS complex of yeast involving thiol blocking agents have been carried out. It was observed that the two types of thiol groups present in the FAS complex could be chemically distinguished. Iodoacetamide 1 alkylated the "peripheral" S_p-thiol group and N-ethylmaleimide 2 alkylated the "central" S_c-thiol group.



1



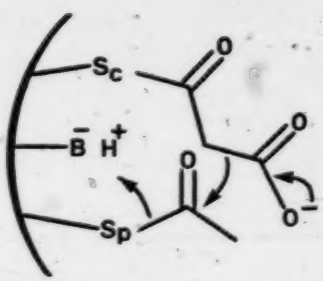
2

Either alkylation inhibited fatty acid biosynthesis. It was interesting that the pH-dependence of the rate of inhibition of the two thiol blocking agents was different. The rate of inhibition of the S_c-thiol group by 2 showed a pH-dependence as expected for an ordinary thiol group. However, the rate of inhibition of the S_p-thiol group by 1 did not change between pH 5 and 9 indicating that this thiol was present as the anion (S_p^-) even at pH 5. The proposed explanation for this result was that the vicinity of the S_p-thiol group included basic groups which could accept the proton thus leaving the S_p-thiol unprotonated. The S_c-thiol group showed normal thiol behaviour as the pantetheine unit would isolate the thiol group from protein interactions. The identity of the basic groups near the S_p-thiol site are presently unknown.

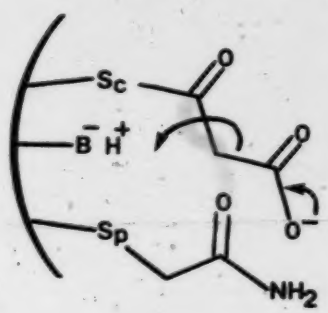
The iodoacetamide blocked S_p-thiol of the FAS brought about a

new enzymic reaction involving decarboxylation of malonyl-CoA to form acetyl-CoA. An explanation given for this process was that when the S_p-thiol site was blocked, no acyl unit was available for condensation and instead protonation occurs (see below). This result indirectly supports the decarboxylation mechanism.

A hypothetical scheme proposed by Lynen for the active site of the condensing enzyme is shown below. The chemical identity of the group or groups responsible for the actual chemistry of the condensation and decarboxylation in the active site of this enzyme remain to be established.



C-Acylation

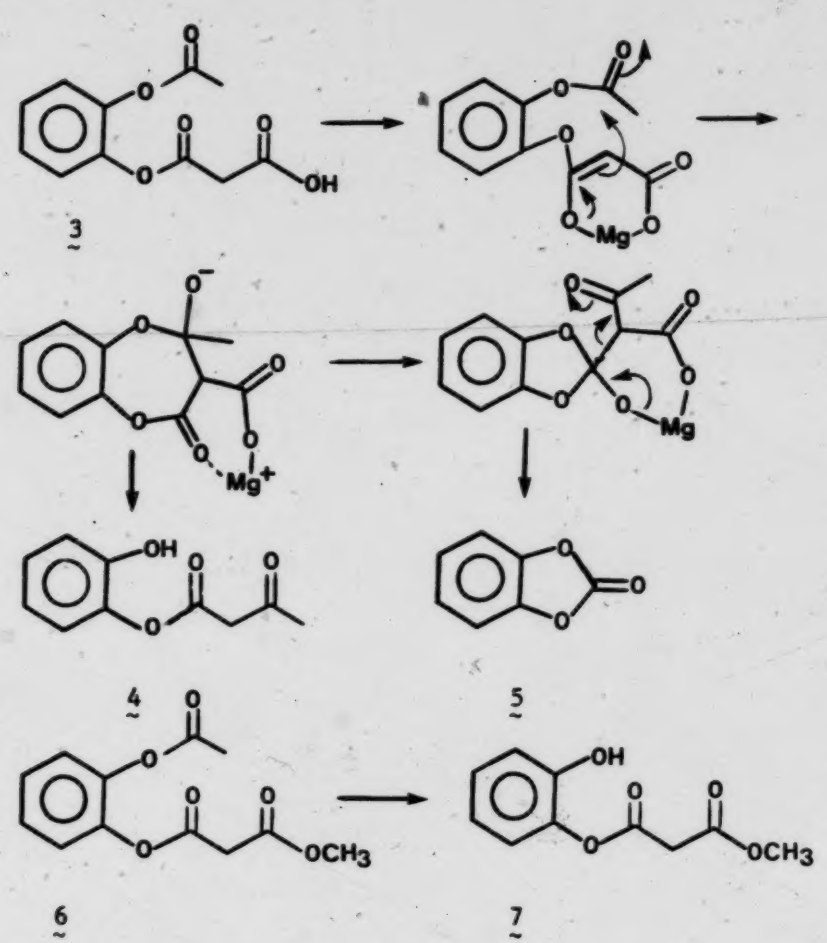


Decarboxylation

CHAPTER 3

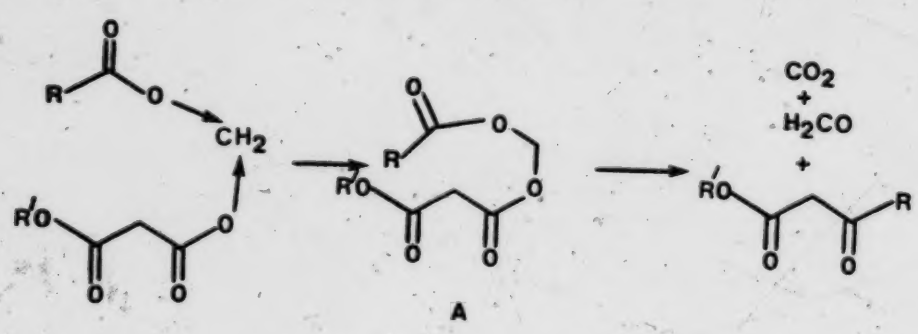
MODEL SYSTEMS FOR C-ACYLATION

The key feature of the biosynthetic C-acylation appears to be the use of malonate. Scott and coworkers[14] used catechol acetate malonate 3 as a model for the condensing enzyme in the fatty acid synthetase complex. When 3 was treated with two equivalents of isopropyl magnesium bromide two products, catechol monoacetoacetate 4 (30%) and catechol carbonate 5 (40%) were isolated. The reaction scheme which the authors proposed is shown below. When the methyl ester 6 was



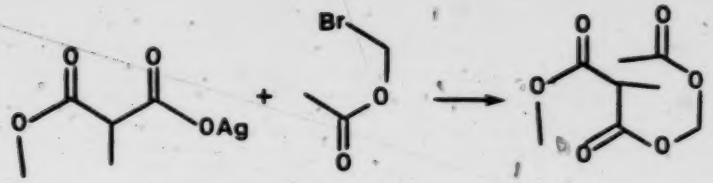
used under the same conditions the products were starting material and catechol monomethylmalonate 7. In the successful acetyl transfer, the magnesium chelation played a role of controlling C versus O-acylation. The use of other bases such as sodium hydride, triethylamine, or *n*-butyl lithium failed to give any acyl transfer product 4. Treatment of 3 with one equivalent of isopropyl magnesium bromide gave no acetyl transfer at room temperature and heating this mixture resulted in decarboxylation to catechol diacetate indicating that a concerted decarboxylative acetyl transfer did not occur.

An alternative for intramolecular acyl transfer incorporating a malonyl group was conceived as a potentially useful method for C-acylation. A simple methylene connection of acyl and malonyl units could provide a six membered transition state for intramolecular C-acylation with the extrusion of formaldehyde and carbon dioxide providing the thermodynamic driving force.

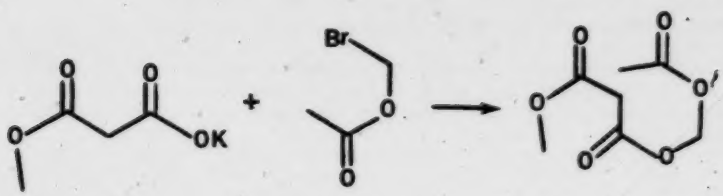


An efficient method to construct the triester system A was developed by the reaction of the bromoester 8[15] with various salts of a malonic half acid ester. The silver salt 9 reacted with 8 to

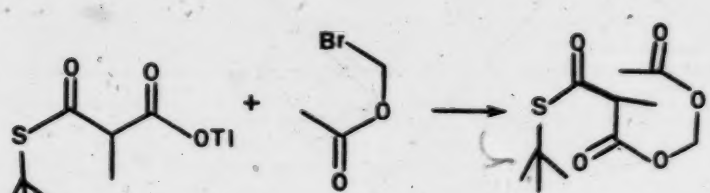
give the triester 10. The potassium salt 11 also reacted with 8 but much more slowly to give the triester 12 and the thallium salt 13 was also effective but gave a poorer yield of the triester 14 (see experimental).



9 8 10



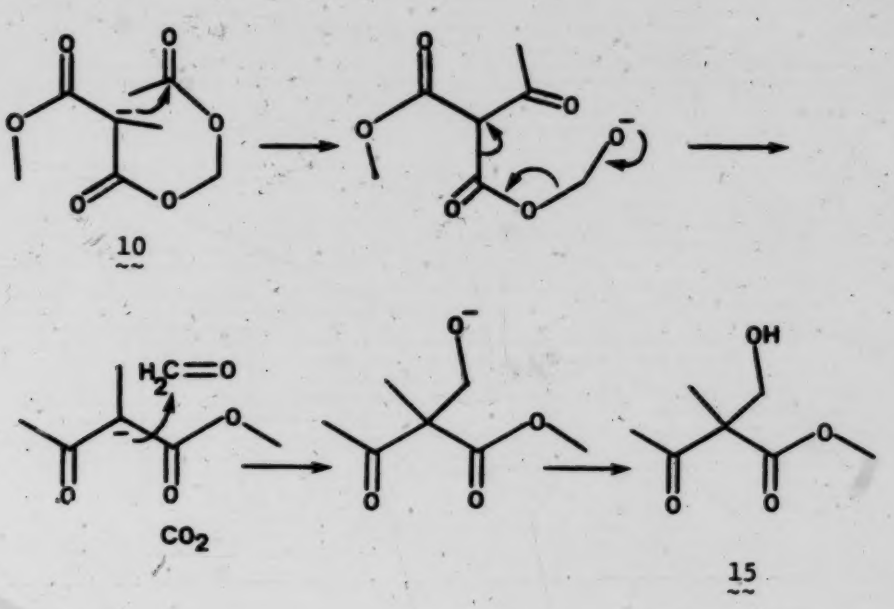
11 8 12



13 8 14

With the triester system prepared, base catalyzed intramolecular C-acylation was investigated. The triester 10 was treated with one equivalent of lithium diisopropylamide at -78°C and was allowed to warm over 1 h to 0°C. Quenching with acetic acid gave recovered starting material in 80% yield. This reaction was repeated and this time the solution was stirred at room temperature for 20 h after which aqueous

acidic workup gave a 93% yield of 15. The structure of the product was readily established by its spectral properties (see experimental). A rational for this result involves an intramolecular acyl transfer followed by condensation of the resulting enolate anion with the formaldehyde generated as shown below.

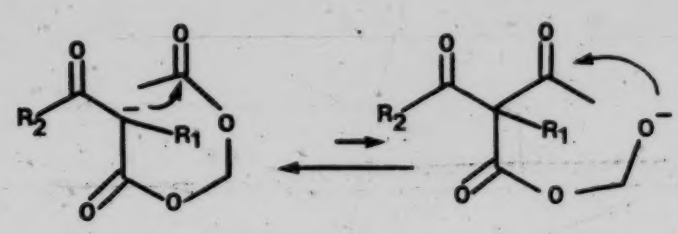


10 15

Performing the same reaction by first generating the enolate of 10 at -78°C, then adding one equivalent of benzylamine and allowing the mixture to stand at room temperature for the required time gave the same product 15 in 90% yield. The benzylamine did not trap formaldehyde.

Treatment of the triesters 12 or 14 with lithium diisopropylamide (1 equiv, room temperature) for 24 h resulted in only recovered starting material in quantitative yield after an aqueous workup. This was surprising in view of the previous result and might be rationalized

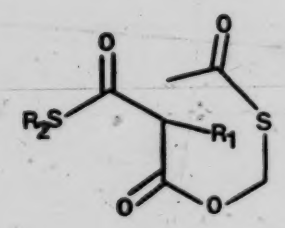
as due to the enhanced stability of the enolate anion of 12 and 14 compared to that of 10 which possibly disfavors the formation of the more basic alcoholate anion as shown. This intramolecular C-acylation



12 $R_1 = H$, $R_2 = OCH_3$

14 $R_1 = CH_3$, $R_2 = St\text{-}Bu$

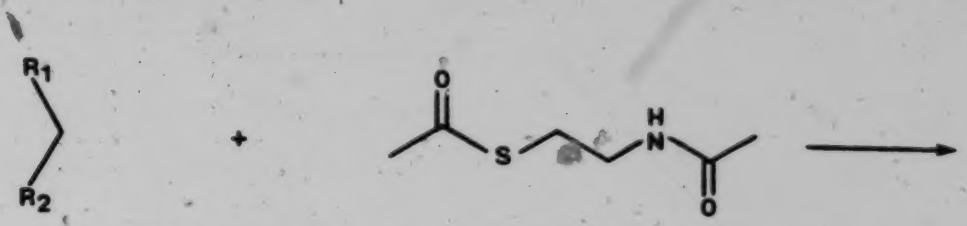
was slow for 10 and therefore 12 and 14 may require heating and/or longer reaction times to effect this reaction. A modification which might facilitate this reaction would be to use a thioester as in 16 (which is a closer model for the biological process) but this idea was not tested.



16

This type of intramolecular C-acylation appeared to be limited in scope and was also complicated by the concurrent alkylation of the formaldehyde generated. Therefore this method was not pursued any further.

Kinetic studies by Lienhard and Jencks[16] showed that acidic methylene compounds 17a-c reacted with N,S-diacyl cysteamine 18 at 25°C in aqueous solution near pH 9. Further, a catalytic effect of added imidazole was demonstrated by a 2000 fold increase in the reaction rate.

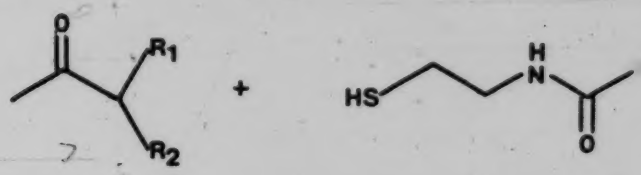


17a R_1 = CN, R_2 = CN

17b R_1 = CN, R_2 = $COSCH_2CH_2NHCOCH_3$

17c R_1 = CN, R_2 = $COOC_2H_5$

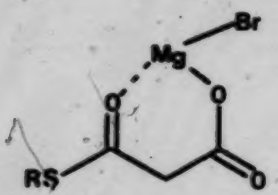
18



This work suggested that an enolate mechanism for the biosynthetic C-acylation was chemically feasible although Lynen favored the decarboxylative mechanism (see p. 183).

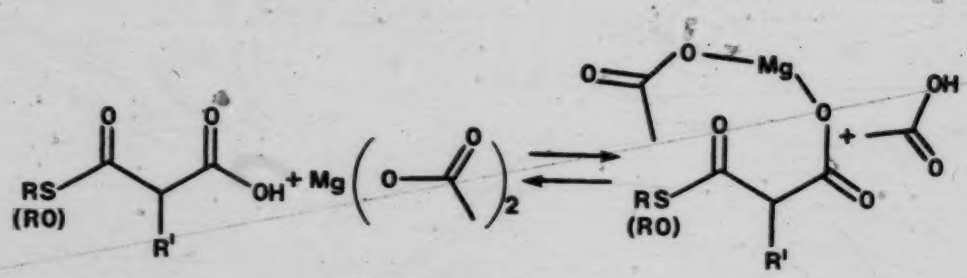
The use of malonyl-CoA in fatty acid biosynthesis and the malonate synthesis of Ireland,[5] described previously, suggested that a malonyl half acid ester was a good choice for the nucleophilic species to develop a mild C-acylation reaction. Treatment of a malonyl half acid ester with only one equivalent of isopropylmagnesium bromide would form the magnesium salt B. The acidity of the methylene group of B might be enhanced by the covalent nature of the O-Mg bond and also by possible magnesium coordination with the β-ester group. Therefore, weak bases

might generate a synthetically useful amount of the enolate anion of B which would then react with an electrophile such as an acyl derivative.



B

Another method to generate an active methylene compound similar to B without the need for a strong base might be possible by treatment of anhydrous magnesium acetate with a malonyl half acid ester to establish an equilibrium as shown, providing a simple source of the magnesium malonyl half acid ester reagents of type I.



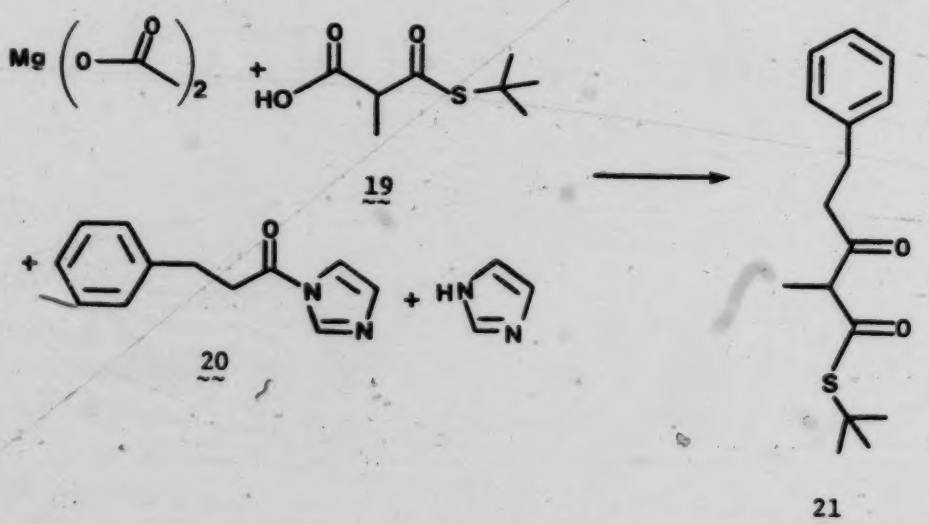
I

The equilibrium would be predicted to favor the formation of I due to the enhanced acidity of the malonic acid compared to acetic acid,

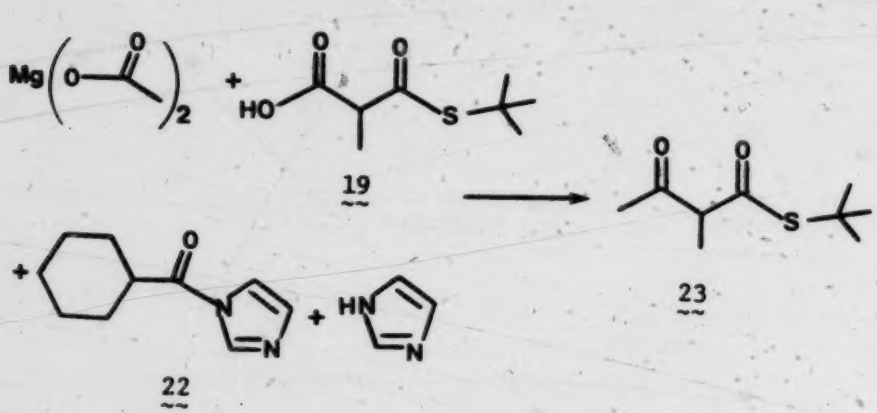
With a potential nucleophilic species chosen, attention was focused on the choice of the electrophilic acyl unit for the C-acylation reaction. The use of a thiol ester was suggested by the bio-

synthetic process but a more reactive acyl unit was desired. The first choice for the acyl unit was an acid imidazolide for the following reasons: 1) they were readily available by reaction of a carboxylic acid with carbonyldiimidazole under mildly basic conditions,[17] 2) the presence of an equivalent of imidazole could catalyze enolate formation from the active methylene compounds of type I as suggested from the study by Jencks,[16] 3) the imidazole portion of an acid imidazolide becomes a good leaving group when a proton source is available, and 4) the active methylene group of I may serve indirectly as the proton source.

The above considerations led to an investigation of the following reaction. A tetrahydrofuran suspension of magnesium acetate and the half acid thiol ester 19 was added to a solution of the acid imidazolide 20 and imidazole in tetrahydrofuran. After stirring the mixture for 1 day at room temperature a 90% yield of the β-keto ester 21 was obtained after an aqueous workup.



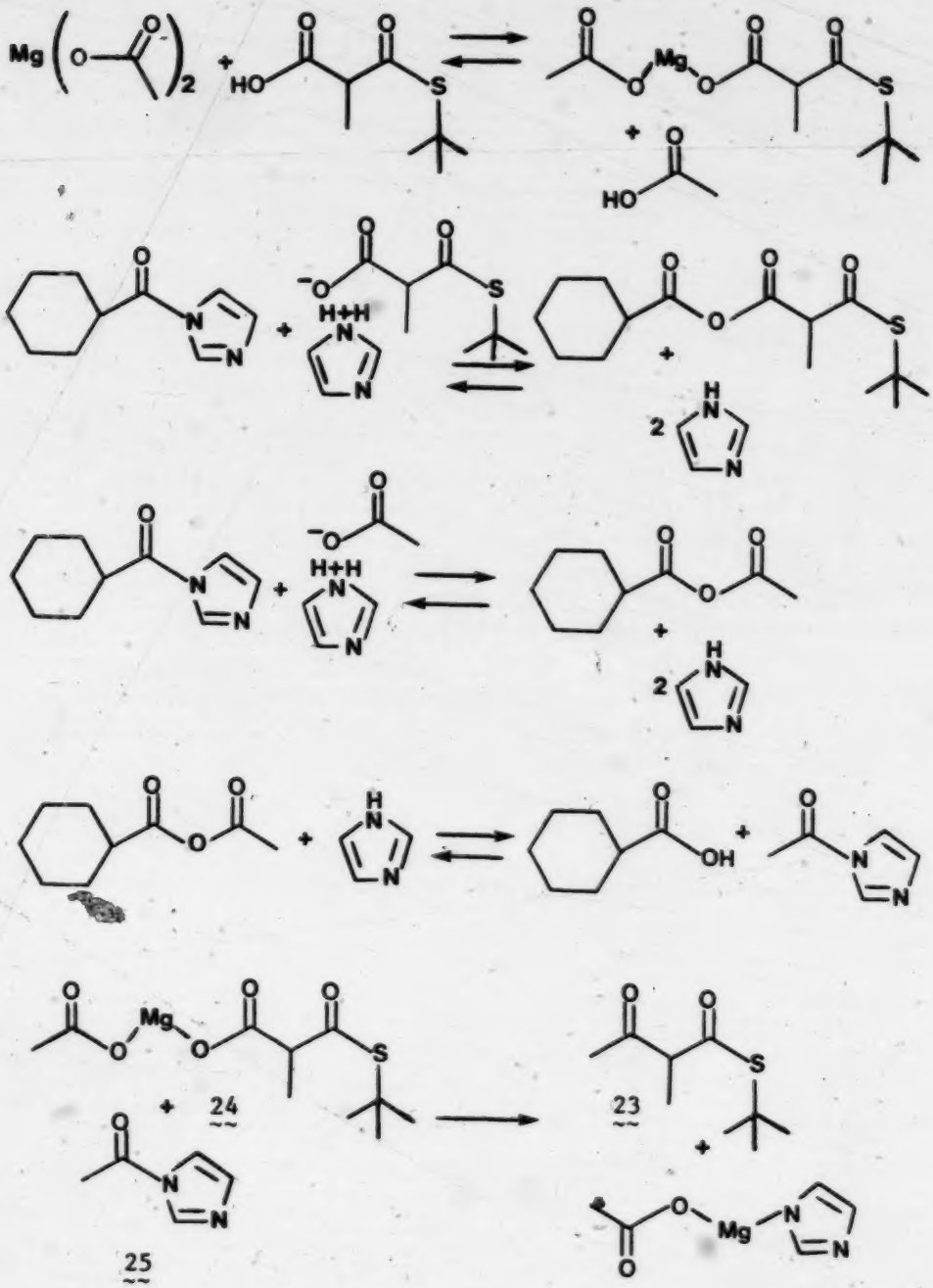
The presence of magnesium acetate was required for the reaction, as shown by a control reaction, where no β-keto ester 21 was formed when the half acid ester 19 was added to the acid imidazolide 20 and imidazole. However, when the reaction was extended to cyclohexanecarboxylic acid imidazolide 22, the major product isolated was 23 in 25% yield. The same reaction was repeated with an additional equivalent



of imidazole and the product 23 was again obtained in 80% yield. This unexpected result indicated that the acetyl group of 23 was derived from the magnesium acetate. This result might be rationalized by a sequence of reversible reactions which are eventually shifted by reaction of the malonate half acid ester magnesium salt 24 with acetic acid imidazolide 25 as shown in Figure 4. Therefore, the reaction of methyl malonyl half acid ester magnesium salt 24 with a secondary carboxylic acid imidazolide chose an alternative reaction pathway. The same result was observed for an attempted reaction with pivalic acid imidazolide which gave an 80% yield of 23 after 12 h at room temperature.

Several other metals were tried to see if this offered any

Figure 4. Proposed Mechanism for the Formation of 23.



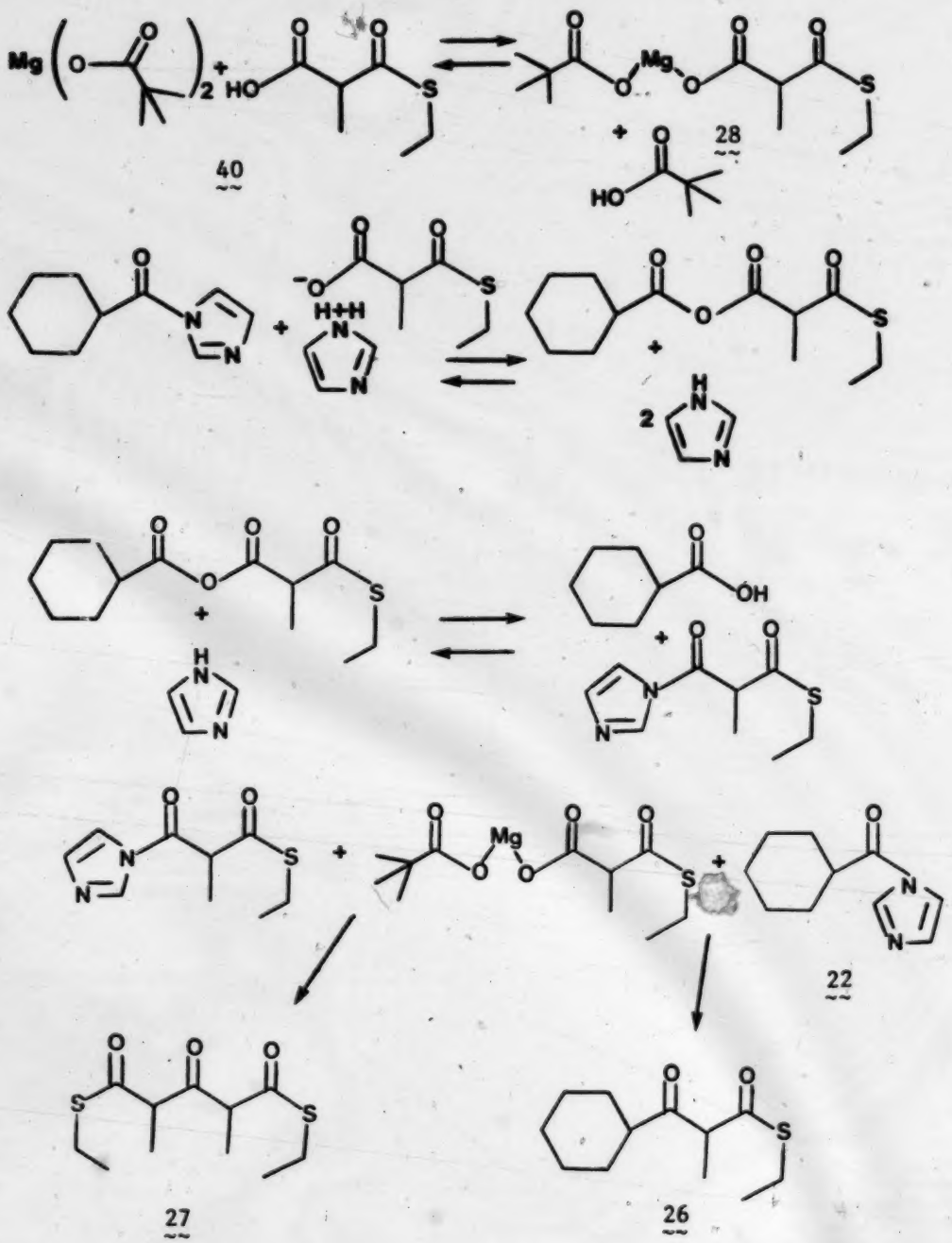
solution. The use of zinc(II) acetate, copper(II) acetate, cobalt(II) acetate, and silver(I) trifluoroacetate showed no promise to effect C-acylation on cyclohexanecarboxylic acid imidazolide 22. Also an attempt with magnesium trifluoroacetate gave no neutral products.

To subdue the acetyl transfer side reaction magnesium pivalate was substituted for magnesium acetate. When the reaction was performed on 22, the desired β-keto ester 26 (20%) was obtained along with a new product 27 (10%). This result might be rationalized by a series of equilibria which eventually leads to two pathways for reaction as shown in Figure 5.

Direct evidence for the exchange of carboxyl groups on magnesium was provided by the preparation of the magnesium salt 28. Azeotropic removal of pivalic acid by slowly evaporating a toluene (50 ml) solution of magnesium pivalate (1 mmol) and methylmalonyl half acid thiol ester 40 (1 mmol) at 50°C and 1.0 mm pressure gave a white solid. The ^{1}H NMR spectrum (tetrahydrofuran-d_8) of this material showed two types of *tert*-butyl groups as broad singlets of equal intensity and an ir spectrum ($CHCl_3$) consistent with the incorporation of one methyl malonic half acid thiol ester group to give 28. Reaction of the magnesium salt 28 (1.0 mmol) with hydrocinnamic acid imidazolide 20 (1.0 mmol) in tetrahydrofuran for 3.5 h gave an 80% yield of the β-keto ester 21 and a 20% yield of recovered hydrocinnamic acid after an aqueous workup.

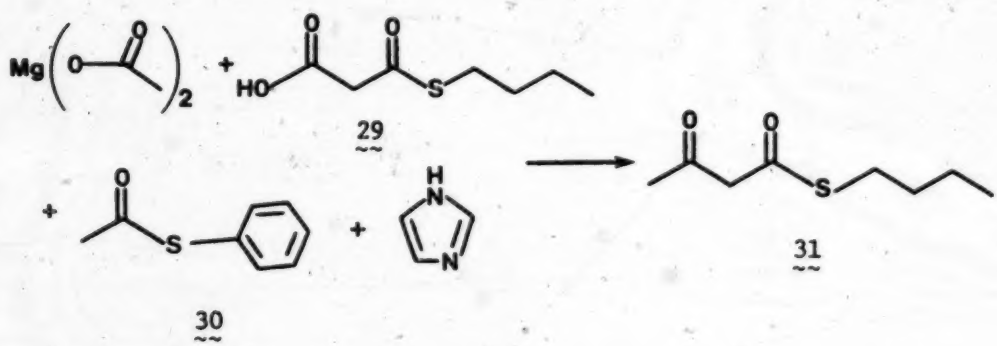
When the magnesium salt 28 was reacted with cyclohexane carboxylic acid imidazolide 22, a mixture of β-keto ester 26 (10%) and diester 27 (20%) was obtained after 6 h at room temperature. This result was similar to the reaction of magnesium pivalate and added

Figure 5. Proposed Mechanism for the Formation of 27.



methylmalonyl half acid thiol ester 19, therefore, the removal of the first equilibrium (formation of the active methylene unit 28) does not seem to offer any significant advantage.

During the course of this work in developing a mild C-acylation reaction, Kobuke and Yoshida[18] reported a similar reaction. They found that malonic half acid *n*-butyl thiol ester 29 reacted with acetic acid benzene thiol ester 30 in the presence of magnesium acetate and imidazole in tetrahydrofuran at room temperature over 3.5 days to give acetoacetic acid *n*-butylthiol ester 31 in 60% yield.



29

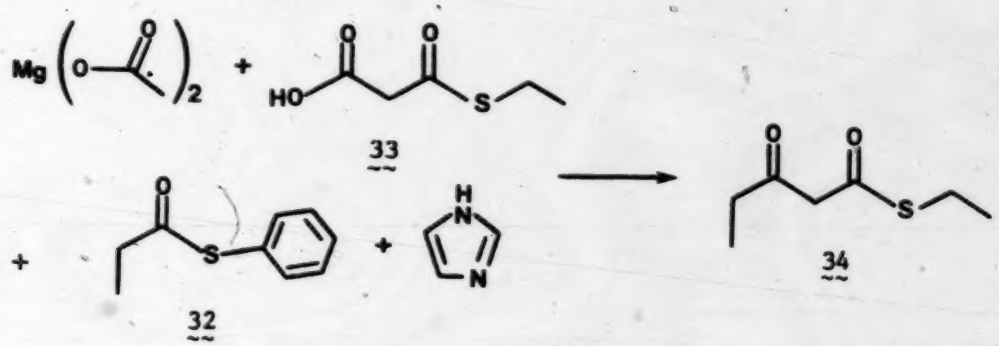
30

31

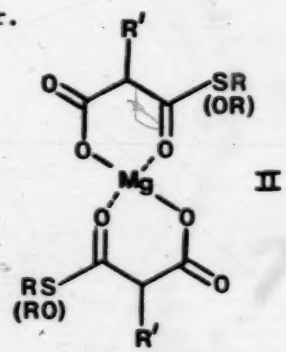
Without either added imidazole or magnesium acetate no reaction was observed.

The pattern of their reaction resembles closely our initial work with magnesium acetate except for the choice of the leaving group in the acyl unit. The source of the acetyl group in their product 31 might not necessarily come from acetic acid benzenethiol ester 30. As was previously described, acetate derived from magnesium acetate was incorporated in the product 23. To check this possibility, Kobuke's reaction was repeated by reacting propionic acid benzenethiol ester 32 (1 mmol) with the malonyl half acid thiol ester 33 (1 mmol) in the

presence of magnesium acetate (1 mmol) and imidazole (1 mmol) in tetrahydrofuran at room temperature for 3 days. The major neutral products isolated after an aqueous workup were 34 and unreacted 32 each in 50% yield. Therefore, no acetate derived from magnesium acetate was incorporated in their case.



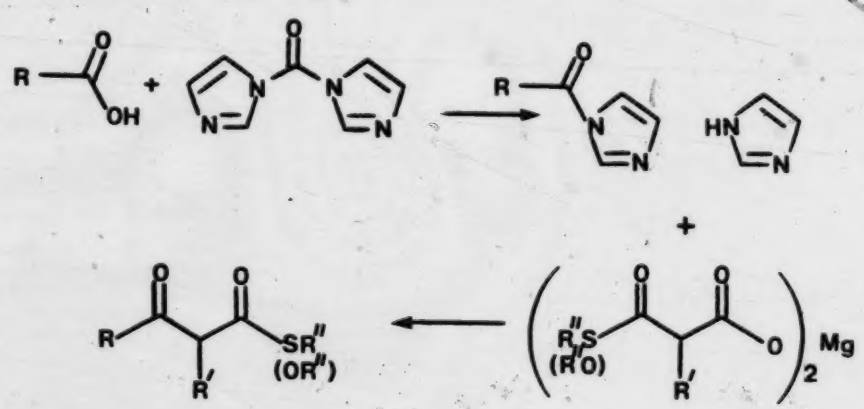
The C-acylation method utilizing magnesium salts of type I was limited in scope and further improvements were obviously needed to provide a synthetically useful procedure. A simple variation by the attachment of two malonic half ester units on magnesium was examined. The magnesium malonyl half acid ester reagents of type II, indeed, provided an efficient reaction with acid imidazolides. The scope of this reaction as a general mild method for C-acylation is described in the next chapter.



CHAPTER 4

MILD C-ACYLATION

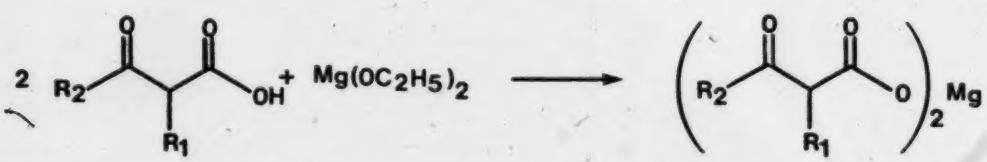
A method for effecting a C-acylation reaction under virtually neutral conditions which demonstrates wide synthetic applicability has been developed. The method used is operationally very simple and involves the successive addition of two reagents to a carboxylic acid in tetrahydrofuran. Carbonyldiimidazole[17] converts the acid into the corresponding acid imidazolide which is, without isolation, treated with the magnesium salt of a malonic or methylmalonic half acid ester to give the corresponding β-keto ester as shown below.



The enolate anions of the esters 35-39 generated with lithium diisopropylamide at -78°C in tetrahydrofuran were carboxylated to give the half acid esters 19, 33, and 40-42.

35	$R_1 = CH_3$, $R_2 = St\text{-Bu}$	19
36	$R_1 = H$, $R_2 = SC_2H_5$	33
37	$R_1 = CH_3$, $R_2 = SC_2H_5$	40
38	$R_1 = H$, $R_2 = OCH_3$	41
39	$R_1 = CH_3$, $R_2 = OCH_3$	42

The magnesium half acid ester reagents 43–47 were prepared by adding magnesium ethoxide (1 equiv) to a solution of the corresponding half acid ester (1 equiv) in tetrahydrofuran followed by filtration of the nearly homogeneous mixture and evaporation of the solvent.



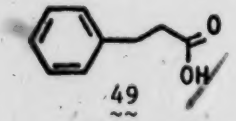
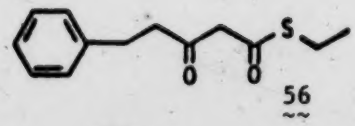
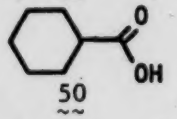
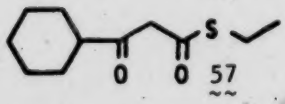
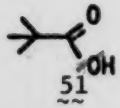
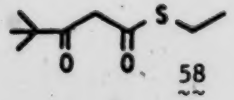
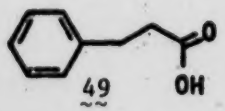
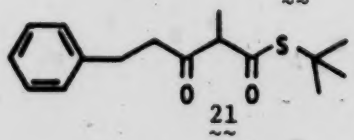
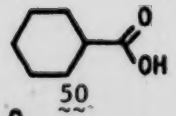
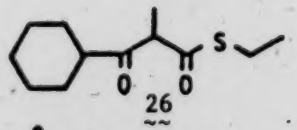
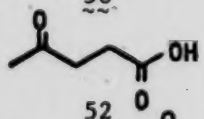
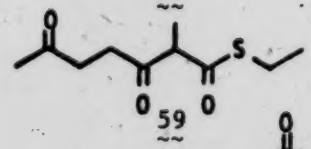
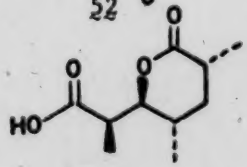
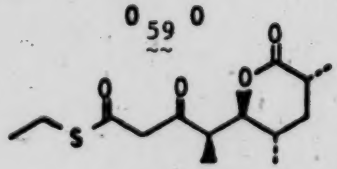
43	$R_1 = CH_3$, $R_2 = St\text{-Bu}$
44	$R_1 = H$, $R_2 = SC_2H_5$
45	$R_1 = CH_3$, $R_2 = SC_2H_5$
46	$R_1 = H$, $R_2 = OCH_3$
47	$R_1 = CH_3$, $R_2 = OCH_3$

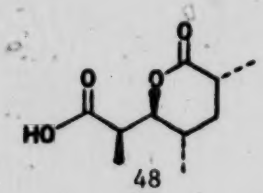
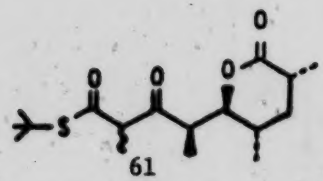
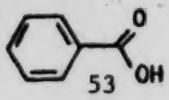
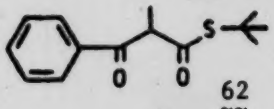
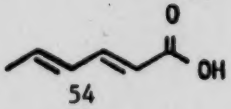
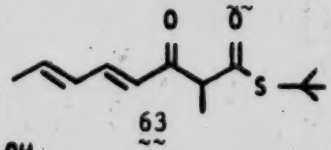
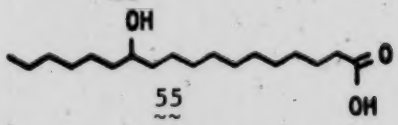
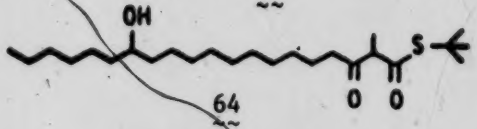
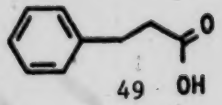
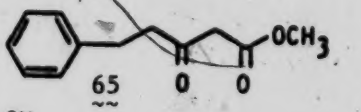
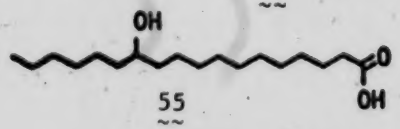
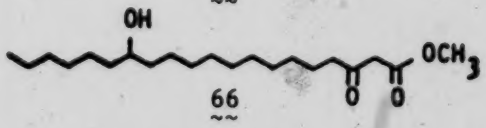
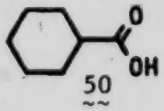
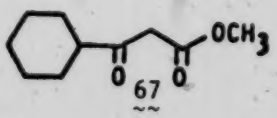
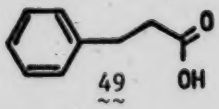
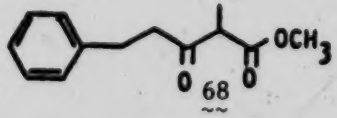
The condensation of these magnesium reagents with an acid imidazolide proceeds in quantitative or excellent yields and is normally complete within 16 h below 35°C. The product β-keto ester is apparently not complexed with magnesium(II). Direct thin layer

chromatography of the reaction mixture after concentration gives the product β-keto ester in the same yield as an aqueous workup. The scope of this method for C-acylation is evident from the results summarized in Table 1. The reaction of reagent 44 proceeds effectively with primary, secondary, and even tertiary carboxylic acids to yield the respective product quantitatively (entries 1-3). Reagent 45 is somewhat less reactive than 44 but gentle warming at 35°C for several hours is adequate to complete the reaction (entry 5). The remarkable feature of this method is manifested in entries 6-8 where acid and base sensitive functionalities survive the condensation conditions. Therefore, addition of an acetate or propionate fragment to levulinic acid and to the Prelog-Djerassi lactonic acid 48[19] proceeds without complication. Unsaturation in both aliphatic and aromatic compounds does not create any problems (entries 9 and 10). The presence of a secondary hydroxyl group as demonstrated for 12-hydroxystearic acid (entry 11) does not hinder the normal course of the reaction. This result is important for the synthesis of polyoxo-macrolides which contain several hydroxyl groups. The removal of the need for hydroxyl protection greatly facilitates the synthetic strategy. This C-acylation reaction works equally well also for the magnesium half acid O-ester reagents 46 and 47 (entries 12-15). By this new C-acylation method, β-keto esters containing a variety of functional groups are now readily accessible.

Further modification has enabled C-acylation to be carried out in the presence of a primary hydroxyl group. Due to the reactivity of a primary hydroxyl group toward carbonyldiimidazole, the previous acylation method is inadequate. A modified procedure circumvents

Table 1. Conversion of Carboxylic Acids into β-Ketoesters.

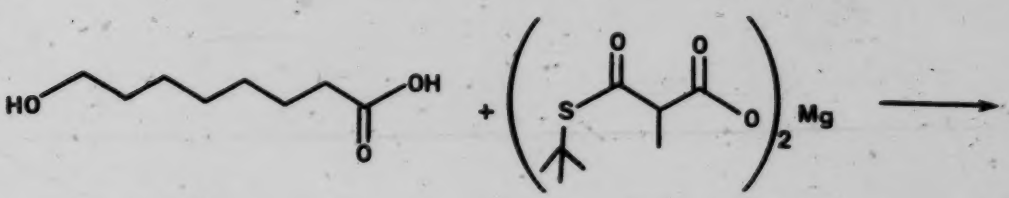
Entry	Carboxylic Acid	Reagent	Conditions[a] (time, temp.°C)	Product	Yield[b](%)
1	 49	44	4h, 25	 56	100
2	 50	44	A	 57	100
3	 51	44	A	 58	100
4	 49	43	A	 21	100
5	 50	45	6h, 35	 26	90
6	 52	45	A	 59	85
7	 48	44	A	 60	88

a	 48	43	B	 61	75
9	 53	43	B	 62	85
10	 54	43	B	 63	95
11	 55	43	A	 64	95
12	 49	46	A	 65	100
13	 55	46	A	 66	95
14	 50	46	A	 67	85
15	 49	47	A	 68	95

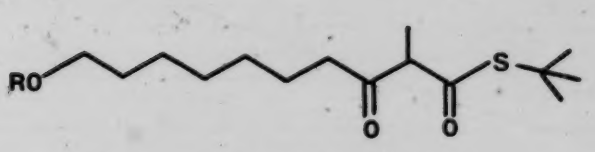
[a]Condition A : 18h at 25°C
Condition B : 24h at 35°C

[b]Yield of isolated, pure product

the use of carbonyldiimidazole and is illustrated for 8-hydroxyoctanoic acid 69. Treatment of the hydroxy acid 69 (1 mmol) in tetrahydrofuran with excess imidazole (4.4 mmol) and trifluoroacetic anhydride (2.2 mmol) provides the corresponding trifluoroacetoxy acid imidazolide 70 which reacts with the magnesium half acid ester reagent 43 (1.2 mmol) to give the trifluoroacetoxy β-keto ester 71. The trifluoroacetate group is readily removed by methanolysis in the presence of sodium acetate (25°C, 2 h) to give the hydroxy β-keto ester 72 in excellent yield.

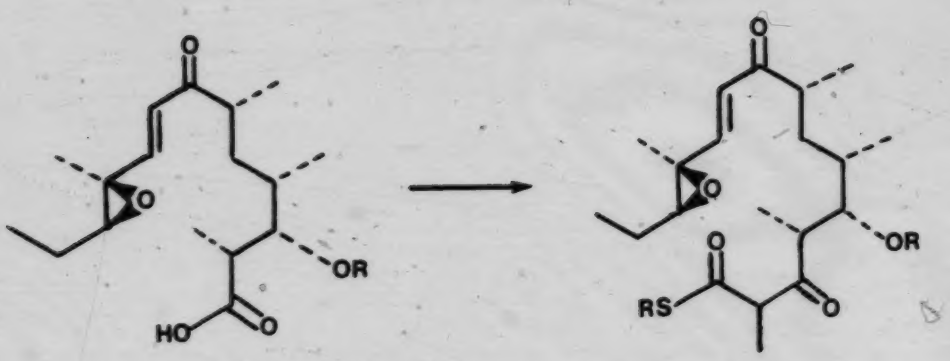


69 43

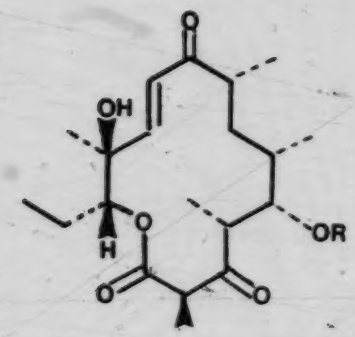


71 R = $COCF_3$
72 R = H

The synthetic versatility of this method for C-acylation has been demonstrated. The application of this method for the synthesis of macrolide antibiotics can be recognised in a hypothetical synthesis of pikronolide 73, the aglycone of pikromycin 74. Conversion of the synthetic seco-acid precursor 75, available from the methymycin synthesis,[19] to the β-keto thioester 76 by the C-acylation method which has been described, followed by epoxide opening, lactonization,[20] and removal of the hydroxyl protection would give pikronolide 73.



75 76



73 R = H

74 R = desosaminyl

Several interesting features observed from various investigations of this new C-acylation reaction and the extent to which it might mimic a similar process in fatty acid biosynthesis are discussed as follows.

A. The Choice of the Electrophilic Acyl Group.

Surprisingly, reactive acid derivatives such as acid chlorides and trifluoroacetic acid mixed anhydrides did not react with the magnesium reagents of type II to give β-keto esters even in the presence of pyridine or triethylamine (2 equiv). The corresponding carboxylic acid was recovered after an aqueous workup. However, if imidazole (2 equiv) was used as the base, the reaction proceeded in the usual fashion to give β-keto esters in excellent yield.

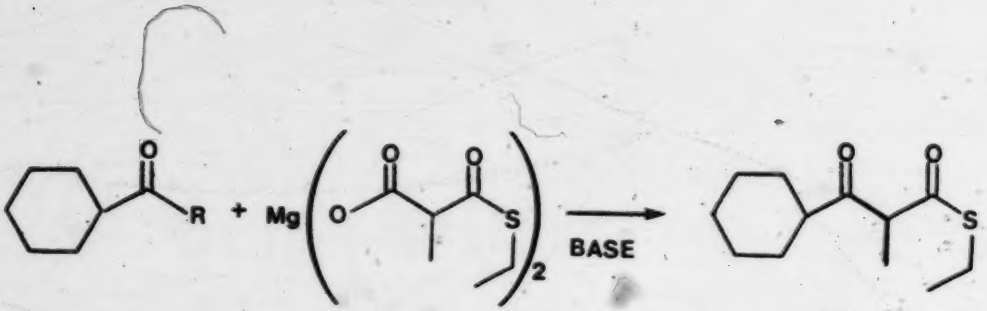
No reaction occurred between the magnesium reagents of type II (for example 45) and the thiol ester 77 or benzothiazolethiol ester 78. However, when imidazole (1.1 equiv) was added to the above mixtures, the β-keto thiol ester 26 slowly formed.

The C-acylation reaction likely proceeded in these cases through the intermediacy of the acid imidazolide. These results indicate a unique relationship between the magnesium reagents of type II, the acid imidazolide, and imidazole and are summarized in Figure 6.

B. The Role of Ligands on Magnesium.

The coordination of various groups on magnesium seems to play a role in the activity of the magnesium half acid ester reagents as previously demonstrated by the difference in reactivity of reagents of type I and type II. The activity of the previously proposed magnesium

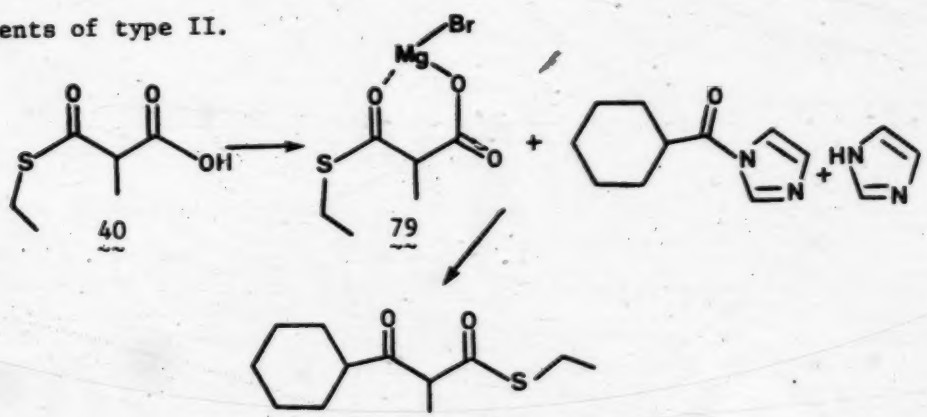
Figure 6. Choice of the Acyl Group for C-Acylation.



26

R	BASE	
-Cl $-O_2CCF_3$	pyridine or triethylamine	X
	imidazole	→
-S- (77)	none	X
-S- (78)	imidazole	→

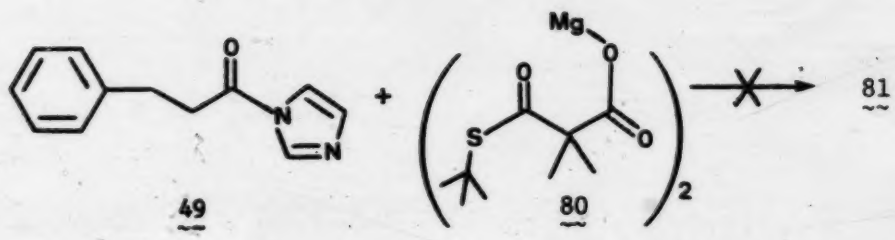
salt 8 was tested. A tetrahydrofuran solution of the magnesium salt 79 was prepared by adding one equivalent of isopropylmagnesium bromide to the thiol ester 40. This solution was then added to cyclohexanecarboxylic acid imidazolide and stirred at 35°C for 24 h. A 50% yield of the corresponding β-keto ester 26 was obtained after an aqueous workup. Therefore, this magnesium salt appears to effect the C-acylation in a similar manner but is less efficient than the magnesium reagents of type II.



26

C. The Mechanistic Course of the C-Acylation Reaction

Whether this new C-acylation reaction proceeds through an enolate or a decarboxylative mechanism cannot be established with the experimental results presently available. Two observations tend to indicate that the enolate anion derived from the magnesium reagent is involved in this condensation: 1) Attempted reaction of the magnesium salt of dimethylmalonic half acid thiol ester 80 with the acid imidazolide of hydrocinnamic acid 49 in the presence of imidazole did not give any of the desired β-keto ester 81. This is indirect evidence that a decarboxylation mechanism is not occurring in this reaction but a possible steric inhibition cannot be excluded.



49 80

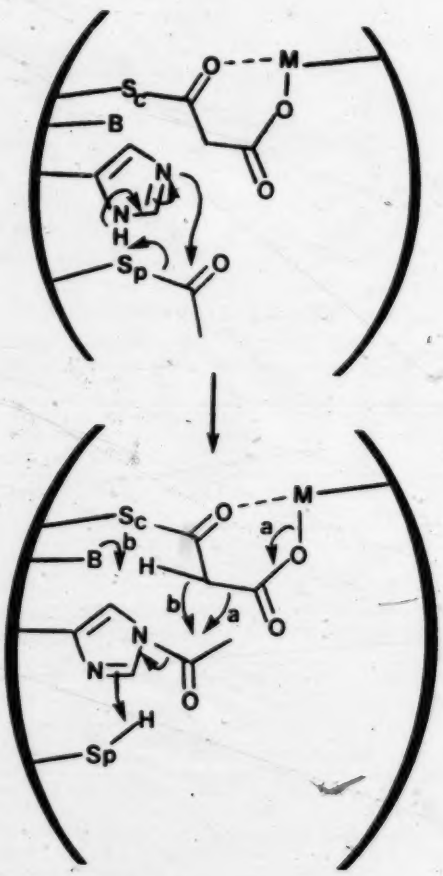
2) The presence of imidazole in the reaction mixture is necessary for initiation of the C-acylation reaction. When the acid imidazolide of cyclohexane carboxylic acid was isolated free from imidazole by extraction with pentane, no reaction with the magnesium salt 45 was observed after one day at room temperature but after addition of imidazole (1 equiv) the reaction proceeded normally.

The decarboxylative mechanism proposed by Lynen and coworkers (see p. 183) represents an unknown reaction in organic chemistry. At the present time, no evidence for this type of mechanism has been found in our C-acylation reaction and the elucidation of the mechanism remains a task for further studies.

D. The Biological Implications

The efficiency and mildness of this new C-acylation reaction suggests that a similar process might be feasible and also identifies possible chemical entities for the yet unknown groups responsible for the actual chemistry in the active site of the condensing enzyme of the fatty acid synthase complex. The condensing enzyme might bind the

malonyl unit in a manner as to enhance the acidity of the methylene group with or without the use of magnesium(II) and the acyl unit could in turn be activated by an imidazole group of a nearby histidine residue. A hypothetical scheme for the active site of the condensing enzyme is shown below, although both magnesium and histidine have not been identified in the active site.



a decarboxylation mechanism

b enolate mechanism

Application of this new, mild C-acylation reaction to the synthesis of polyoxo-macrolide antibiotics and further synthetic extensions of this method will likely be forthcoming in the near future.

CHAPTER 5

EXPERIMENTAL

All experiments were conducted under an inert atmosphere of dry argon or nitrogen. The solvents and reagents used in each experiment were dried and purified by accepted procedures.[21]

A rotary evaporator (water aspirator vacuum) was used for the removal of solvents where "evaporation under reduced pressure" is mentioned.

The spectral data, ^{1}H NMR, ir, and mass spectra were obtained and are reported as described in Part I.

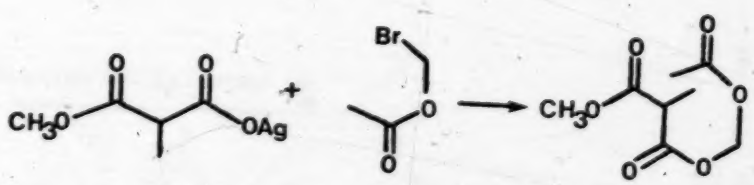
Thin layer chromatography was performed using EM-Merk^R, HF 254 and 366 (type 60) silica gel without binder as described in Part I.

Preparation of the Silver Salt 9.

42 9

To a suspension of silver carbonate (1.40 g, 5.1 mmol) in water (50 ml) was added half acid ester 42 (1.32 g, 10 mmol) and the mixture was stirred in the dark for 48 h. The mixture was filtered through Celite and the clear aqueous filtrate was evaporated at reduced pressure to give a white solid. Toluene (20 ml) was added and the suspension was evaporated at reduced pressure, followed by vacuum pumping at 1.0 mm for 24 h to give 2.1 g of 9 as a white powder. This product was stored in the dark in a desiccator over P_2O_5.

Preparation of Triester 10.

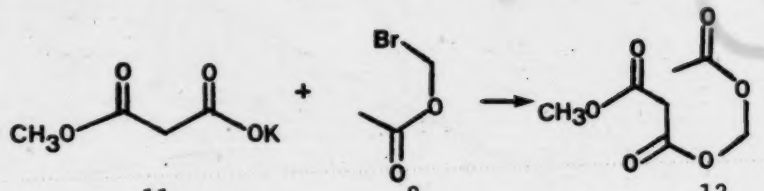


9 8 10

To a suspension of the silver salt 9 (240 mg, 1.0 mmol) in acetone (5 ml) was added bromoester 8 (160 mg, 1.0 mmol) and the mixture was stirred for 2 h in the dark. The mixture was filtered through Celite and evaporated to give 190 mg (90%) of 10 as a colorless oil.

^{1}H NMR ($CDCl_3$) δ: 1.42 (d, J=7.0 Hz, 3), 2.10 (s, 3), 3.49 (q, J=7.0 Hz, 1), 3.72 (s, 3), 5.75 (s, 2).

Preparation of Triester 12.



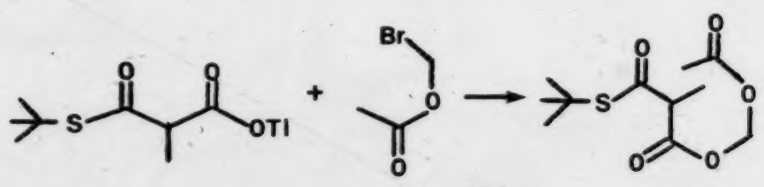
11 8 12

The bromo ester 8 (1.7 g, 11 mmol) was added to a suspension of the potassium salt 11 (1.6 g, 10 mmol) in acetone (25 ml) and the mixture was stirred for 3 days at room temperature. The mixture was filtered and the filtrate was evaporated at reduced pressure to give 1.7 g (90%) of 12 as a colorless oil.

ir (CCl_4) cm^{-1} : 3000 (w), 2960 (w), 1770 (s), 1750 (s), 1440 (m), 1375 (m), 1215 (br m), 1140 (br m), 1020 (br m).

^{1}H NMR ($CDCl_3$) δ: 2.09 (s, 3), 3.42 (s, 2), 3.72 (s, 3), 5.74 (s, 2).

Preparation of Triester 14.



13 8 14

Thallium compounds are very toxic and should be handled accordingly.

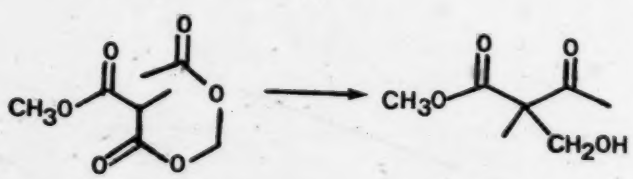
Thallium ethoxide (2.5 g, 10 mmol) was added slowly to a solution

of half acid thioester 19 (1.9 g, 10 mmol) in benzene (25 ml). The mixture was stirred for 30 min at room temperature and the solvent was then evaporated at reduced pressure. The residue was dissolved in benzene (20 ml) and the bromoester 8 (1.7 g, 11 mmol) was added. A white precipitate appeared immediately. The mixture was stirred for 15 min, then filtered through Celite and the filtrate was evaporated at reduced pressure. The residue was dissolved in chloroform (5 ml) and column chromatographed (silica gel, 50 g) with chloroform to give 1.5 g (58%) of 14 as a colorless oil.

ir (CCl_4) cm^{-1} : 3000 (w), 2960 (m), 1765 (s), 1680 (s), 1460 (m), 1370 (m).

^1H NMR ($CDCl_3$) δ: 1.40 (d, J=7.0 Hz, 3), 1.48 (s, 9), 2.09 (s, 3), 3.59 (q, J=7.0 Hz, 1), 5.72 (s, 2).

Intramolecular Acylation to 15.



10 15

A solution of lithium diisopropylamide (1.3 ml, 0.5 M, 0.66 mmol) in tetrahydrofuran was added to a solution of the triester 10 (136 mg, 0.66 mmol) at -78°C in tetrahydrofuran. The mixture was allowed to warm to room temperature and was stirred for 20 h. Aqueous 5% HCl (2 ml) was added followed by ether (25 ml). The organic extract was washed with saturated NaCl (20 ml), dried (Na_2SO_4), filtered and evaporated at reduced pressure to give a colorless oil. Purification of this product

by ptlc (silica gel, 30% ethyl acetate in hexane) gave 95 mg (93%) of 15.

ir (CCl_4) cm^{-1} : 3400–2700 (br), 3000 (m), 2960 (m), 1750 (s), 1710 (s), 1240 (br s), 1130 (br m), 1050 (s).

^1H NMR ($CDCl_3$) δ: 1.46 (s, 3), 2.09 (s, 3), 3.72 (br s, 4), 4.4 (s, 2).

mass spectrum, m/e : calculated for $C_7H_{12}O_4$ = 160.0736,
observed 160.0728.

C-Acylation with Magnesium Reagents of Type I, Preparation of 21.

19 21

Carbonyldiimidazole (160 mg, 1.0 mmol) was added to a solution of hydrocinnamic acid (150 mg, 1.0 mmol) in tetrahydrofuran (5 ml) and the mixture stirred for 4 h at room temperature. This solution was then added to a suspension of anhydrous magnesium acetate (150 mg, 1.0 mmol) and half acid thiol ester 19 (190 mg, 1.0 mmol) in tetrahydrofuran (5 ml). The mixture became homogeneous and was stirred for 24 h at room temperature. The solvent was evaporated and the residue was dissolved in ether (20 ml) and aqueous 0.5 N HCl (20 ml). The ether layer was separated and the aqueous phase was further extracted with ether (10 ml). The combined ether extract was washed with aqueous saturated $NaHCO_3$, dried (Na_2SO_4), filtered, and evaporated at reduced pressure to give 250 mg (90%) of 21 as a colorless oil.

ir (CCl_4) cm^{-1} : 3040 (w), 2980 (w), 1730 (s), 1680 (s), 1610 (w), 1460 (m), 1370 (m).

^1H NMR ($CDCl_3$) δ: 1.28 (d, J=7.0 Hz, 3), 1.45 (s, 9), 1.87 (br s, 4), 3.62 (q, J=7.0 Hz, 1), 7.20 (m, 5).

mass spectrum, m/e : 278.1340 (19, $m^+ = C_{16}H_{22}O_2S$), 189.0904 (28, $C_{12}H_{13}O_2$), $C_{12}H_{13}O_2$), 162.1044 (47, $C_{11}H_{14}O$), 133.0655 (73, C_9H_9O), 91.0548 (94, C_7H_7), 57.0721 (100, C_4H_9).

49 23

Carbonyldiimidazole (162 mg, 1.0 mmol) was added to a solution of cyclohexanecarboxylic acid (130 mg, 1.0 mmol) in tetrahydrofuran (5 ml) and the mixture was stirred for 24 h at room temperature. This solution was added to a suspension of magnesium acetate (150 mg, 1.0 mmol) and half acid thiol ester 19 (190 mg, 1.0 mmol) and the resulting homogeneous solution was stirred for 16 h at room temperature. Aqueous workup as before (p.213) gave 85 mg (45%) of 23 as a colorless oil as the only neutral product.

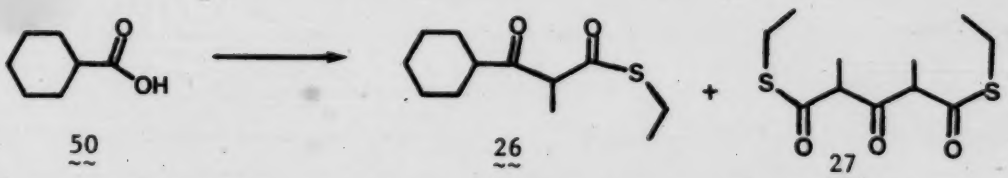
ir (CCl_4) cm^{-1} : 2960 (m), 1725 (s), 1680 (s), 1460 (m), 1370 (m).

^1H NMR ($CDCl_3$) δ: 1.29 (d, J=7.0 Hz, 3), 1.44 (s, 9), 2.18 (s, 3), 3.59 (q, J=7.0 Hz, 1).

Preparation of Magnesium Pivalate

Magnesium ethoxide (1.1 g, 9.6 mmol) was added to a solution of pivalic acid (2.0 g, 19.6 mmol) in tetrahydrofuran (20 ml). The mixture gradually became homogeneous and after stirring for 1 h the solvent was evaporated. The white solid residue was heated at 100°C at 1.0 mm pressure for 4 h and was then stored at room temperature in a dessicator.

C-Acylation with Magnesium Reagents of Type I, Preparation of 26.



50 26 27

Carbonyldiimidazole (160 mg, 1.0 mmol) was added to a solution of cyclohexanecarboxylic acid (130 mg, 1.0 mmol) in tetrahydrofuran (5 ml) and the mixture was stirred for 12 h at room temperature. This solution was then added to a solution of magnesium pivalate (230 mg, 1.0 mmol) and the half thiol ester 40 (160 mg, 1.0 mmol) in tetrahydrofuran (5 ml) and the resulting homogeneous mixture was stirred for 16 h at room temperature. The solvent was evaporated and the residue was dissolved in ether (20 ml) and aqueous 0.5 N HCl (20 ml). The ether layer was separated and the aqueous phase was further extracted with

with ether (10 ml). The combined ether extract was washed with aqueous saturated $NaHCO_3$, dried (Na_2SO_4), filtered, and evaporated at reduced pressure to give a colorless oil. Purification of the product by ptlc (silica gel, 10% ethyl acetate in hexane) gave 45 mg (20%) of 26 (rf = 0.4) and 22 mg (8%) of 27 (rf = 0.3).

26

ir (CCl_4) cm^{-1} : 2940 (s), 2860 (m), 1720 (s), 1680 (s), 1460 (m).

^1H NMR ($CDCl_3$) δ: 1.10-2.0 [1.25 (t, J=7.5 Hz), 1.34 (d, J=7.0 Hz), m, 16], 2.55 (m, 1), 2.90 (9, J=7.5 Hz, 2), 3.89 (q J=7.0 Hz, 1).

mass spectrum, m/e : 228.1186 (12, $m^+ = C_{12}H_{20}O_2S$), 111.0804 (44, $C_7H_{11}O$), 83.0858 (100, C_6H_{11}).

27

ir (CCl_4) cm^{-1} : 2980 (m), 2940 (m), 2880 (w), 1740 (s), 1680 (s), 1610 (s), 1460 (m), 970 (s).

^1H NMR ($CDCl_3$) δ: 1.25 (t, J=7.5 Hz, 6), 1.36 (d, J=7.0 Hz, 6), 2.89 (q, J=7.5 Hz, 4), 4.03 (q, J=7.0 Hz, 2).

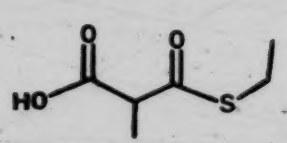
General Procedure for the Preparation of the Half Acid Esters 19, 33, 40 - 42, and 82.

A hexane solution of *n*-butyllithium (162 ml, 1.6 M, 0.26 mol) was added to a solution of diisopropylamine (36.6 ml, 0.26 mol) in tetrahydrofuran (500 ml) at -40°C. The solution was stirred for 15 min after which it was cooled to -78°C and the ester to be carboxylated (0.24 mol) was added slowly dropwise. The mixture was stirred at -78°C for 30 min and then an excess of dry ice pellets (~100 g, 2.3 mol) was added. The mixture was allowed to warm to room temperature and the solvent was evaporated at reduced pressure. The residue was suspended in cold (5°C) water (250 ml) and was acidified by dropwise addition of concentrated HCl to a pH of 2. The aqueous mixture was extracted with ether (2 x 250 ml). The ether layer was extracted with aqueous saturated $NaHCO_3$ (2 x 150 ml) and the aqueous extract at 0°C was acidified to pH 3 by dropwise addition of cold 6 N HCl with stirring. The aqueous phase was extracted with ether (2 x 200 ml) and the ether extract was washed with aqueous saturated NaCl, dried (Na_2SO_4), filtered, and evaporated at reduced pressure to give the half acid ester in about 70% yield. It was shown to be pure by NMR spectroscopy.

33

ir ($CHCl_3$) cm^{-1} : 3300 - 2800 (br), 3010 (m), 1725 (s), 1680 (s).

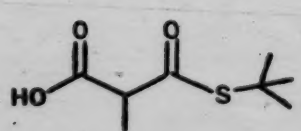
^1H NMR ($CDCl_3$) δ: 1.27 (t, J=6.5 Hz, 3), 2.95 (q, J=6.5 Hz, 2), 3.60 (s, 2), 10.95 (s, 1).



40

ir ($CHCl_3$) cm^{-1} : 3400 - 2600 (br), 3000 (br), 2940 (m), 1720 (s), 1680 (s), 1460 (m), 1220 (br m), 970 (s).

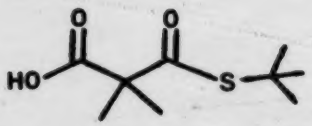
^1H NMR ($CDCl_3$) δ: 1.26 (t, J=7.0 Hz, 3), 1.45 (d, J=6.5 Hz, 3), 2.92 (q, J=7.0 Hz, 2), 3.65 (q, J=6.5 Hz, 1), 10.65 (s, 1).



19

ir ($CHCl_3$) cm^{-1} : 3400-2600 (br), 2980 (m), 1720 (s), 1680 (s), 1460 (m), 1370 (m), 1220 (br m), 965 (s).

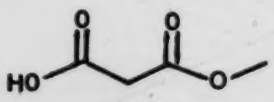
^1H NMR ($CDCl_3$) δ: 1.41 (d, J=7.0 Hz, 3), 1.48 (s, 9), 3.60 (q, J=7.0 Hz, 1), 10.08 (s, 1).



82

ir ($CHCl_3$) cm^{-1} : 3400-2600 (br), 2980 (m), 1760 (s), 1675 (s), 1470 (m), 1370 (m), 1290 (m), 1170 (m), 970 (m).

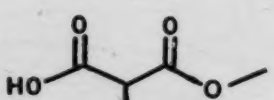
^1H NMR ($CDCl_3$) δ: 1.42 (s, 15), 11.15 (s, 1).



41

ir ($CHCl_3$) cm^{-1} : 3300-2700 (br), 3010 (m), 2960 (w), 1750 (s), 1720 (s), 1440 (m), 1220 (br).

^1H NMR ($CDCl_3$) δ: 3.40 (s, 2), 3.72 (s, 3), 10.60 (s, 1).



42

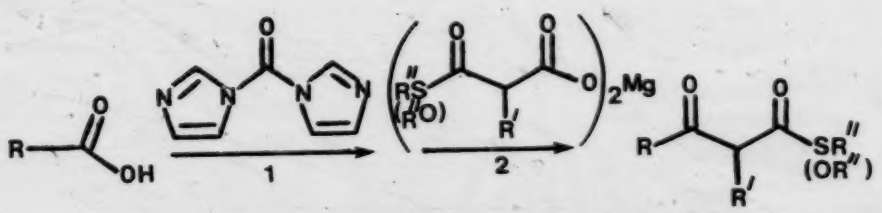
ir ($CHCl_3$) cm^{-1} : 3300-2700 (br), 3010 (br m), 2960 (m), 1740 (br s), 1720 (br s), 1460 (m), 1220 (br m).

^1H NMR ($CDCl_3$) δ: 1.45 (d, J=7.0 Hz, 3), 3.55 (q, J=7.0 Hz, 1), 3.79 (s, 3), 10.13 (s, 1).

Preparation of Magnesium Reagents of Type II.

To a solution of 10 mmol of half acid ester in tetrahydrofuran (25 ml) was added 5 mmol of freshly prepared magnesium ethoxide. The mixture was stirred for about 1 h during which time a near homogeneous solution formed. The mixture was filtered through a pad of Celite and the filtrate was evaporated at reduced pressure to give a white solid residue. After pumping under vacuum (0.1 mm, 5 h) a white solid reagent was obtained which was ready for use.

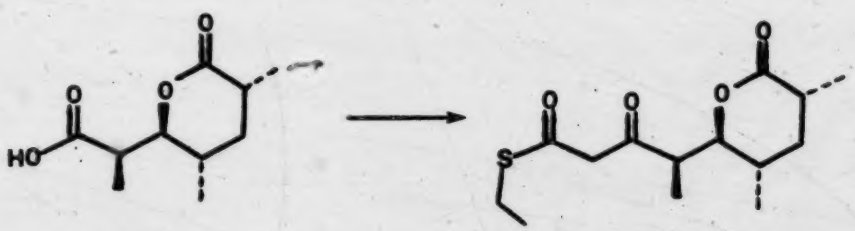
General Method for C-Acylation.



Carbonyldiimidazole (1.1 mmol) was added to a solution of a carboxylic acid (1.0 mmol) in tetrahydrofuran (2 ml) and the mixture was stirred for at least 6 h at room temperature. The magnesium salt of a malonic or methylmalonic half acid ester (1.1 mmol) was added and the mixture was stirred at room temperature overnight (16 h) or until the reaction was complete (see Table 1, p. 203). The solvent was evaporated at reduced pressure and the residue was either directly chromatographed on silica gel to isolate the pure product or subjected to the following aqueous workup. The residue was dissolved in ether (20 ml)

and aqueous 0.5 N HCl (20 ml) and the layers were separated. The aqueous phase was further extracted with ether (10 ml). The combined ether extract was washed with aqueous saturated $NaHCO_3$ (20 ml), dried (Na_2SO_4), filtered, and evaporated at reduced pressure to give the corresponding β-keto ester in quantitative or excellent yield. The esters were shown to be pure by ^1H NMR and TLC analysis.

C-Acylation of Lactonic Acid 48.



48 60

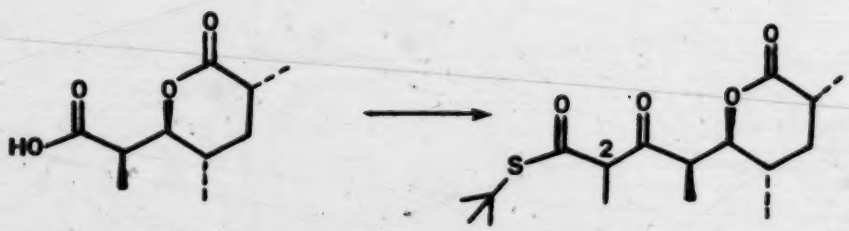
To a solution of lactonic acid 48 (100 mg, 0.5 mmol) in tetrahydrofuran (5 ml) was added carbonyldiimidazole (90 mg, 0.55 mmol). The mixture was stirred at room temperature for 8 h after which the magnesium salt 44 (190 mg, 0.6 mmol) was added. After stirring for 24 h the solvent was evaporated and the residue was extracted with ether (20 ml) and aqueous 0.5 N HCl (10 ml). The organic phase was separated, washed with aqueous saturated $NaHCO_3$ (10 ml), dried (Na_2SO_4), filtered, and evaporated to give 145 mg of a pale yellow oil. Purification by ptlc (silica gel, 20% ethyl acetate in hexane) gave 125 mg (88%) of 60

ir (CCl_4) cm^{-1} : 2980 (m), 2940 (m), 2880 (w), 1740 (s), 1680 (m), 1620 (s), 1460 (m), 1380 (m).

^1H NMR ($CDCl_3$) δ: 0.9-1.7 (m, 12), 1.5-2.2 (m, 3) 2.5 (sept, J=6.4, 1), 2.7-3.0 (m, 3), 3.80 (ABq, J=15.0 Hz, 1.3), 4.35 (dd, J=10.0 Hz, J=2.5 Hz, 0.35), 4.53 (dd, J=10.0 Hz, J= 2.5 Hz, 0.65), 5.54 (s, 0.35), 35% enol form was

present.

mass spectrum, m/e : 286.1241 (10, $m^+ = C_{14}H_{22}O_4S$), 225.1127 (82, $C_{12}H_{17}O_4$), 183.1022 (31, $C_{10}H_{15})_3$), 127.0759 (100, $C_7H_{11})_2$).



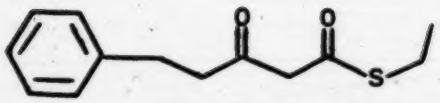
48 61

The same procedure as for 60 was used with substitution of the magnesium salt 43. An aqueous workup was not used but instead the solution was concentrated to about 1 ml and was subjected directly to ptlc (silica gel, 2.0 mm, 20% ethyl acetate in hexane) to give (75%) of 61 as a mixture of epimers at C2.

ir (CCl_4) cm^{-1} : 2960 (s), 2920 (s), 2860 (m), 1740 (br s), 1670 (br s), 1450 (m), 1370 (m), 1160 (br m).

^1H NMR ($CDCl_3$) δ: 1.0-1.5 (m, 12), 1.48 (s, 9), 1.6-2.2 (m, 3), 2.5 (m, 1), 2.96 (m, 1), 3.80 (m, 1), 4.50 (dd, J=10.0 Hz, J=3.0 Hz, 0.5), 4.60 (dd, J=10.0 Hz, J=3.0 Hz, 0.5).

mass spectrum, m/e : 239.1288 (42, m^+ - *tert*-butyl = $C_{13}H_{19}O_4$), 212.1413 (63, $C_{12}H_{20})_3$), 183.1023 (23, $C_{10}H_{15}O_3$), 155.1071 (19, $C_9H_{15})_2$), 57.0721 (100, C_4H_9).

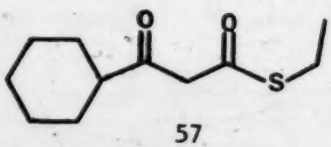


56

ir (CCl_4) cm^{-1} : 3040 (w), 2980 (w), 2940 (w), 1730 (m), 1675 (m), 1620 (br s), 1460 (w), 1190 (m), 1100 (s).

^1H NMR ($CDCl_3$) δ: 1.22 (t, J=7.5 Hz, 2.7), 1.26 (t, J=7.5 Hz, 0.3), 2.84 (m, 4), 3.58 (s, 1.4), 5.37 (s, 0.3), 7.18 (m, 5).

mass spectrum, m/e : 236.0869 (33.5, $C_{13}H_{16}O_2S$), 175.0759 (67, $C_{11}H_{11}O_2$), 105.0703 (90, C_8H_9), 91.0550 (100, C_7H_7).

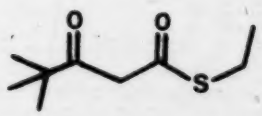


57

ir (CCl_4) cm^{-1} : 2940 (s), 2860 (m), 1720 (m), 1680 (m), 1620 (br s), 1460 (m), 1175 (m), 1090 (s).

^1H NMR ($CDCl_3$) δ: 1.30 (m, 9), 1.5-2.2 (m, 4), 2.50 (m, 1), 2.94 (q, J=7.5 Hz, 2), 3.72 (s, 1.4), 5.40 (s, 0.3); 30% enol form was present.

mass spectrum, m/e : 214.1026 (36, $m^+ = C_{11}H_{18}O_2S$), 153.0915 (100, $C_9H_{13}O_2$), 111.0809 (46, $C_7H_{11}O$).

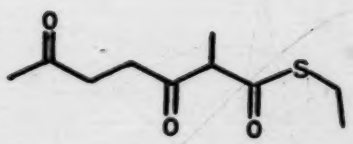


58

ir (CCl_4) cm^{-1} : 2980 (m), 2940 (w), 2880 (w), 1730 (m), 1680 (m), 1610 (br s), 1400 (m), 1370 (m), 1270 (m), 1100 (s), 900 (s).

^1H NMR ($CDCl_3$) δ: 1.12 (s, 1.8), 1.14 (s, 7.2), 1.24 (t, J=7.5 Hz, 2.4), 1.26 (t, J=7.5 Hz, 0.6), 2.90 (q, J=7.5 Hz, 2), 3.72 (s, 1.6), 5.44 (s, 0.3); ∿ 30% enol form was present.

mass spectrum, m/e : 131.0164 (5, m^+ - *tert*-butyl = $C_5H_7O_2S$), 127.0757 (9, $m^+ - SC_2H_5 = C_7H_{11}O_2$), 57.0719 (100, C_4H_9).

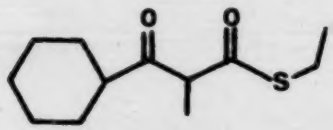


59

ir (CCl_4) cm^{-1} : 2980 (br m), 2940 (m), 2880 (w), 1720 (s), 1670 (s).

^1H NMR ($CDCl_3$) δ: 1.26 (t, J=7.5 Hz, 3), 1.38 (d, J=7.0 Hz, 3), 2.16 (s, 3), 2.75 (m, 4), 2.91 (q, J=7.5 Hz, 2), 3.82 (q, J=7.0 Hz, 1).

mass spectrum, m/e : 216.0819 (1, $m^+ = C_{10}H_{16}O_3S$), 155.0707 (58, $C_8H_{11}O_3$), 99.0445 (100, $C_5H_7O_2$).

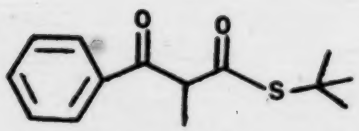


26

ir (CCl_4) cm^{-1} : 2940 (s), 2860 (m), 1720 (s), 1680 (s), 1460 (m).

^1H NMR ($CDCl_3$) δ: 1.10–2.0 [1.25 (t, J=7.5 Hz), 1.34 (d, J=7.0 Hz), m, 16], 2.55 (m, 1), 2.90 (q, J=7.5 Hz, 2), 3.89 (q, J=7.0 Hz, 1).

mass spectrum, m/e : 228.1186 (12, $m^+ = C_{12}H_{20}O_2S$), 111.0804 (44, $C_7H_{11}O$), 83.0858 (100, C_6H_{11}).

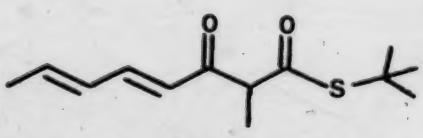


62

ir (neat) cm^{-1} : 2980 (m), 1700 (s), 1670 (s), 1600 (w), 1450 (m), 1370 (m), 1225 (m), 960 (s).

^1H NMR ($CDCl_3$) δ: 1.41 (s, 9), 1.48 (d, J=7.0 Hz, 3), 4.51 (9, J=7.0 Hz, 1), 7.50 (m, 3), 8.0 (dd, J=8.0 Hz, J=2.0 Hz, 2).

mass spectrum, m/e : 250.1024 (5.5, $m^+ = C_{14}H_{18}O_2S$), 194.0396 (21, $C_{10}H_{10}O_2S$), 134.0729 (51, $C_9H_{10}O$), 105.0336 (100, C_7H_5O), 77.0395 (41, C_6H_5), 57.0720 (76, C_4H_9).

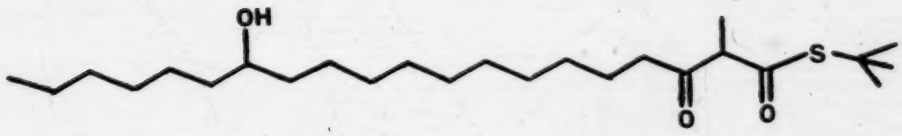


63

ir (neat) cm^{-1} : 2970 (m), 2940 (m), 1690 (s), 1670 (s), 1640 (s), 1600 (s), 1460 (s), 1370 (m), 1340 (m), 1005 (s), 950 (br s).

^1H NMR ($CDCl_3$) δ: 1.36 (d, J=7.0 Hz, 3), 1.48 (s, 9), 1.88 (d, J=5.0 Hz, 3), 3.85 (q, J=7.0 Hz, 1), 6.24 (m, 3), 7.28 (m, 1).

mass spectrum, m/e : 240.1188 (10, $m^+ = C_{13}H_{20}O_2S$), 184.0556 (29, $C_9H_{11}O_2S$), 151.0756 (13, $C_9H_{11}O_2$), 95.0493 (100, C_6H_7O).

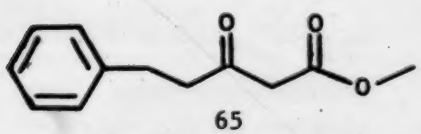


64

ir (CCl_4) cm^{-1} : 3500-3100 (br), 2940 (s), 2860 (m), 1765 (m), 1725 (s), 1700 (s), 1675 (s), 1470 (m).

^1H NMR ($CDCl_3$) δ: 0.88 (m, 3), 1.2-1.8 (m, 31), 1.47 (s, 9), 2.2-2.7 (m, 2), 3.60 (m, 2), 4.46 (br s, 1).

mass spectrum, m/e : 371.2612 (3, m^+ - *tert*-butyl = $C_{21}H_{39}O_3S$), 339.2892 (26, $C_{21}H_{39}O_3$), 321.2793 (37, $C_{21}H_{37}O_2$), 57.0722 (100, (C_4H_9).

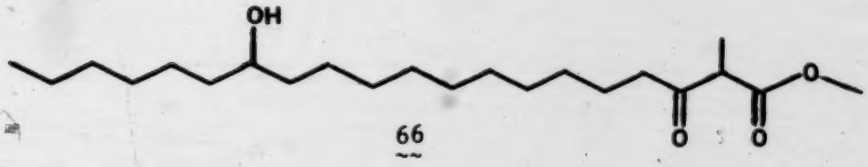


65

ir (CCl_4) cm^{-1} : 3015 (w), 2960 (w), 1750 (s), 1725 (s), 1660 (s), 1630 (s), 1610 (w), 1450 (m), 1440 (m), 1240 (s).

^1H NMR ($CDCl_3$) δ: 2.86 (br s, 4), 3.38 (s, 2), 3.66 (s, 3), 7.20 (m, 5).

mass spectrum, m/e : 206.0937 (28, $m^+ = C_{12}H_{14}O_3$), 105.0696 (45, C_8H_9), 91.0544 (100, C_7H_7).

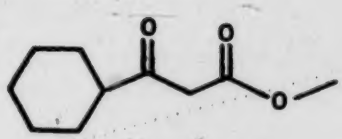


66

ir (CCl_4) cm^{-1} : 3500-3100 (br), 2920 (s), 2860 (s), 1750 (s), 1720 (s), 1660 (m), 1630 (m), 1460 (br m), 1400 (m), 1320 (m), 1300 (m), 1240 (s), 1010 (m).

^1H NMR ($CDCl_3$) δ: 0.85 (m, 3), 1.1-1.8 (m, 28), 2.0 (br, 1), 2.50 (t, J=7.0 Hz, 2), 3.42 (s, 2), 3.54 (m, 1), 3.70 (s, 3).

mass spectrum, m/e : 356.2924 (2, $m^+ = C_{21}H_{40}O_4$), 339.2899 (13, $C_{21}H_{39}O_3$), 271.1917 (52, $C_{15}H_{27}O_4$), 239.1642 (66, $C_{14}H_{23}O_3$), 197.1546 (45, $C_{12}H_{21}O_2$).

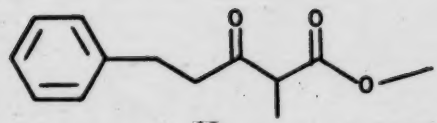


67

ir (CCl_4) cm^{-1} : 2940 (s), 2860 (m), 1750 (s), 1715 (s), 1660 (s), 1630 (s), 1450 (s), 1240 (s), 1230 (s).

^1H NMR ($CDCl_3$) δ: 1.0-2.0 (m, 10), 2.46 (m, 1), 3.48 (s, 2), 3.72 (s, 3).

mass spectrum, m/e : 184.1104 (14, $m^+ = C_{10}H_{16}O_3$), 149.0237 (34, $C_8H_5O_3$), 111.0808 (33, $C_7H_{11}O$), 101.0237 (58, $C_4H_5O_3$), 83.0858 (100, C_6H_{11}).



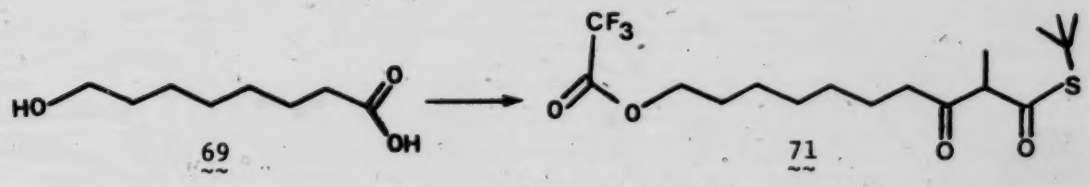
68

ir (CCl_4) cm^{-1} : 3015 (w), 2960 (w), 1750 (s), 1720 (s), 1460 (m), 1440 (m), 1210 (m).

^1H NMR ($CDCl_3$) δ: 1.25 (d, J=7.5 Hz, 3), 2.74 (s, 4), 3.47 (q, J=7.5 Hz, 1), 3.60 (s, 3), 7.15 (s, 5).

mass spectrum, m/e : calculated for $C_{13}H_{16}O_3$ = 220.1099, observed 220.1095.

C-Acylation in the Presence of a Primary Alcohol, Preparation of 71.



69 71

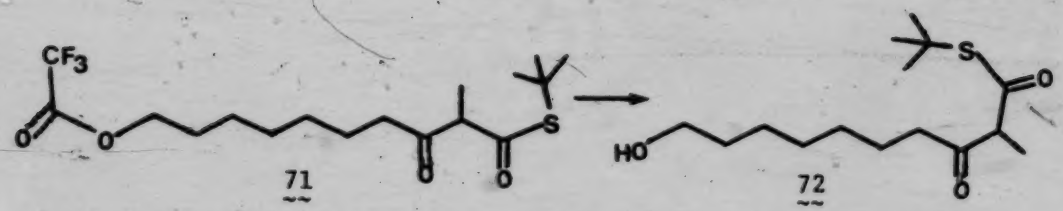
Trifluoroacetic anhydride (320 µl, 2.2 mmol) was added to a solution of 8-hydroxyoctanoic acid (160 mg, 1.0 mmol) and imidazole (300 mg, 4.4 mmol) in tetrahydrofuran (5 ml) and a white precipitate appeared within a few minutes. The mixture was stirred for 30 min at room temperature and then magnesium methylmalonic acid thiol ester 43 (480 mg, 1.2 mmol) was added. After stirring for 16 h at room temperature, the solvent was evaporated and the residue was dissolved in ether (20 ml) and aqueous 0.5 N HCl (20 ml). The ether layer was separated and the aqueous phase was further extracted with ether (10 ml). The combined ether extract was washed with aqueous saturated $NaHCO_3$, dried (Na_2SO_4), filtered, and evaporated to give 365 mg (95%) of 71 as a colorless oil.

ir (CCl_4) cm^{-1} : 2940 (s), 2870 (s), 1790 (s), 1730 (s), 1675 (s), 1460 (br m), 1370 (m), 1230 (s), 1180 (br s).

^1H NMR ($CDCl_3$) δ: 1.2-1.9 [1.29 (d, J=7.0 Hz), 4.45 (s), m, 22], 2.2-2.7 (m, 2), 3.62 (q, J=7.0 Hz, 1), 4.30 (br t, J=7.0 Hz, 2)

mass spectrum, m/e : 384.1587 (1, $m^+ = C_{17}H_{27}O_4SF_3$), 268.1287 (36, $C_{12}H_{19}O_3F_3$), 239.0900 (54, $C_{10}H_{14}O_3F_3$), 57.0717 (100, C_4H_9).

Removal of a Primary Trifluoroacetate, Preparation of 72.



71 72

To a solution of trifluoroacetate 71 (180 mg, 0.5 mmol) in methanol (2 ml) was added sodium acetate (165 mg, 2.0 mmol) and the mixture was stirred for 2 h at room temperature. The solvent was evaporated at reduced pressure and the residue was extracted with ether (10 ml) and filtered. The solids were washed with ether (10 ml) and the filtrate was evaporated at reduced pressure to give 140 mg (97%) of 72 as a colorless oil.

ir (CCl_4) cm^{-1} : 3600-3100 (br), 2940 (s), 2860 (m), 1730 (s), 1675 (s), 1460 (m), 1370 (m).

^1H NMR ($CDCl_3$) δ: 1.1-1.8 [1.24 (d, J=7.0 Hz), 4.45 (s), m, 22], 2.0-2.6 (m, 2), 3.4-3.6 (m, 3), 5.18 (br s, 1).

mass spectrum, m/e : 199.1329 (7, m^+ - S , $C_{11}H_{19}O_3$), 172.1464 (14, $C_{10}H_{20}O_2$), 57.0720 (100, C_4H_9).

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